

## CLINICAL PRACTICE GUIDELINES

# 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Developed in Collaboration With and Endorsed by the American College of Clinical Pharmacy and the Heart Rhythm Society

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**AIM:** The “2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation” provides recommendations to guide clinicians in the treatment of patients with atrial fibrillation.

**METHODS:** A comprehensive literature search was conducted from May 12, 2022, to November 3, 2022, encompassing studies, reviews, and other evidence conducted on human subjects that were published in English from PubMed, EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline. Additional relevant studies, published through November 2022, during the guideline writing process, were also considered by the writing committee and added to the evidence tables, where appropriate.

\*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see Appendix 1 for detailed information. †ACC/AHA Joint Committee on Clinical Practice Guidelines liaison. ‡ACC/AHA Joint Committee on Performance Measures liaison. §Lay stakeholder representative. ¶American College of Clinical Pharmacy representative. ¶Heart Rhythm Society representative. #Joint ACC/AHA staff representative.

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**STRUCTURE:** Atrial fibrillation is the most sustained common arrhythmia, and its incidence and prevalence are increasing in the United States and globally. Recommendations from the “2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation” and the “2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation” have been updated with new evidence to guide clinicians. In addition, new recommendations addressing atrial fibrillation and thromboembolic risk assessment, anticoagulation, left atrial appendage occlusion, atrial fibrillation catheter or surgical ablation, and risk factor modification and atrial fibrillation prevention have been developed.

**Key Words:** AHA Scientific Statements ■ acute coronary syndrome ■ alcohol ■ anticoagulants ■ anticoagulation agents ■ antiplatelet agents ■ apixaban ■ atrial fibrillation ■ atrial flutter ■ cardioversion ■ catheter ablation ■ coronary artery disease ■ coronary heart disease ■ dabigatran ■ edoxaban ■ exercise ■ heart failure ■ hypertension ■ idarucizumab ■ left atrial appendage occlusion ■ myocardial infarction ■ obesity ■ percutaneous coronary intervention ■ pulmonary vein isolation ■ risk factors ■ rivaroxaban ■ sleep apnea ■ stents ■ stroke ■ surgical ablation ■ thromboembolism ■ warfarin

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## TOP 10 TAKE-HOME MESSAGES

1. **Stages of atrial fibrillation (AF):** The previous classification of AF, which was based only on arrhythmia duration, although useful, tended to emphasize therapeutic interventions. The new proposed classification, using stages, recognizes AF as a disease continuum that requires a variety of strategies at the different stages, from prevention, lifestyle and risk factor modification, screening, and therapy.
2. **AF risk factor modification and prevention:** This guideline recognizes lifestyle and risk factor modification as a pillar of AF management to prevent onset, progression, and adverse outcomes. The guideline emphasizes risk factor management throughout the disease continuum and offers more prescriptive recommendations, accordingly, including management of obesity, weight loss, physical activity, smoking cessation, alcohol moderation, hypertension, and other comorbidities.
3. **Flexibility in using clinical risk scores and expanding beyond CHA<sub>2</sub>DS<sub>2</sub>-VASc for prediction of stroke and systemic embolism:** Recommendations for anticoagulation are now made based on yearly thromboembolic event risk using a validated clinical risk score, such as CHA<sub>2</sub>DS<sub>2</sub>-VASc. However, patients at an intermediate annual risk score who remain uncertain about the benefit of anticoagulation can benefit from consideration of other risk variables to help inform the decision, or the use of other clinical risk scores to improve prediction, facilitate shared decision making, and incorporate into the electronic medical record.
4. **Consideration of stroke risk modifiers:** Patients with AF at intermediate to low (<2%) annual risk of ischemic stroke can benefit from consideration of factors that might modify their risk of stroke, such as the characteristics of their AF (eg, burden), nonmodifiable risk factors (sex), and other dynamic or modifiable factors (blood pressure control) that may inform shared decision-making discussions.
5. **Early rhythm control:** With the emergence of new and consistent evidence, this guideline emphasizes the importance of early and continued management of patients with AF that should focus on maintaining sinus rhythm and minimizing AF burden.
6. **Catheter ablation of AF receives a Class 1 indication as first-line therapy in selected patients:** Recent randomized studies have demonstrated the superiority of catheter ablation over drug therapy for rhythm control in appropriately selected patients. In view of the most recent evidence, we upgraded the Class of Recommendation.
7. **Catheter ablation of AF in appropriate patients with heart failure with reduced ejection fraction receives a Class 1 indication:** Recent randomized

studies have demonstrated the superiority of catheter ablation over drug therapy for rhythm control in patients with heart failure and reduced ejection failure. In view of the data, we upgraded the Class of Recommendation for this population of patients.

8. **Recommendations have been updated for device-detected AF:** In view of recent studies, more prescriptive recommendations are provided for patients with device-detected AF that consider the interaction between episode duration and the patient's underlying risk for thromboembolism. This includes considerations for patients with AF detected via implantable devices and wearables.
9. **Left atrial appendage occlusion devices receive higher level Class of Recommendation:** In view of additional data on safety and efficacy of left atrial appendage occlusion devices, the Class of Recommendation has been upgraded to 2a compared with the 2019 AF Focused Update for use of these devices in patients with long-term contraindications to anticoagulation.
10. **Recommendations are made for patients with AF identified during medical illness or surgery (precipitants):** Emphasis is made on the risk of recurrent AF after AF is discovered during noncardiac illness or other precipitants, such as surgery.

## PREAMBLE

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 writing and review efforts. Guidelines are the official policy of the ACC and AHA. For some guidelines, the ACC and AHA collaborate with other organizations.

## 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 Joint Committee on Clinical Practice Guidelines (Joint Committee) continuously reviews, updates, and modifies guideline methodology on the basis of published standards from organizations, including the Institute of Medicine,<sup>1,2</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 health care professionals at the point of care.

Numerous modifications to the guidelines have been implemented to make them 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.

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>3</sup>

To ensure that guideline recommendations remain current, new data will be reviewed on an ongoing basis by the writing committee and staff. Going forward, targeted sections/knowledge chunks will be revised dynamically after publication and timely peer review of potentially practice-changing science. The previous designations of “full revision” and “focused update” will be phased out. For additional information and policies on guideline development, readers may consult the ACC/AHA guideline methodology manual<sup>4</sup> and other methodology articles.<sup>5–7</sup>

## Selection of Writing Committee Members

The Joint Committee strives to ensure that the guideline writing committee contains requisite content expertise and is representative of the broader cardiovascular community by selection of experts across a spectrum of backgrounds, representing different geographic regions, sexes, races, ethnicities, intellectual perspectives/biases, and clinical practice settings. Organizations and profes-

sional societies with related interests and expertise are invited 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' comprehensive and relevant RWI; for the purposes of full transparency, comprehensive and relevant disclosure information for the Joint Committee 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>4,5</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  $\geq 1$  questions deemed of utmost clinical importance and 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 time frame 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 (GDMT) 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.

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Chair, ACC/AHA Joint Committee on  
Clinical Practice Guidelines*

## 1. INTRODUCTION

### 1.1. Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence based. An initial extensive evidence review, which included literature derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline, was conducted from May 2022 to November 2022. Key search words included but were not limited to the following: atrial fibrillation; pregnancy; heart defects, congenital; smoking; cardiomyopathy, hypertrophic; alcohol; caffeine; sleep; diet; fitness; obesity; anticoagulants; diabetes; rhythm monitoring; heart failure; genetics; heart valve diseases; rate control; catheter ablation; social determinants of health; chronic kidney disease; sinus rhythm; chronic coronary syndromes; left atrial appendage occlusion; left atrial appendage exclusion; cardiac surgical procedures; amiodarone; electrical cardioversion; thromboembolism; rhythm control; Wolff-Parkinson-White syndrome. Additional relevant studies, published through November 2022 during the guideline writing process, were also considered by the writing committee and added to the evidence tables when appropriate. The final evidence tables are included in the [Online Data Supplement](#) and summarize the evidence used by the writing committee to formulate recommendations. References selected and published in the present document are representative and not all-inclusive.

### 1.2. Organization of the Writing Committee

The writing committee consisted of cardiologists, cardiac electrophysiologists, surgeons, pharmacists, and patient representatives/lay stakeholders. The writing committee included representatives from the ACC and AHA, ACCP, and HRS. Appendix 1 of the current document lists writing committee members' comprehensive and relevant RWI.

### 1.3. Document Review and Approval

The Joint Committee appointed a peer review committee to review the document. The peer review committee comprised individuals nominated by the ACC, AHA, and the collaborating organizations. Reviewers' RWI information was distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC and the AHA and was endorsed by ACCP and HRS.

**Table 1. Associated ACC/AHA Guidelines**

Title	Organization	Publication Year (Reference)
<b>Guidelines</b>		
Atrial fibrillation	AHA/ACC/HRS	2019 <sup>1*</sup> 2014 <sup>2</sup>
Atrial fibrillation	ESC/EACTS/EHRA	2021 <sup>3</sup>
Atrial fibrillation	CCS	2020 <sup>4</sup>
Management of adults with congenital heart disease	AHA/ACC	2018 <sup>5</sup>
Diagnosis and treatment of patients with hypertrophic cardiomyopathy	AHA/ACC	2020 <sup>6</sup>
Management of patients with valvular heart disease	ACC/AHA	2021 <sup>7</sup>
Coronary artery revascularization	ACC/AHA/AATS/STS/SCAI	2021 <sup>8</sup>
Evaluation and diagnosis of chest pain	AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR	2021 <sup>9</sup>
Prevention of stroke in patients with stroke and transient ischemic attack	AHA/ASA	2021 <sup>10</sup>
Management of heart failure	AHA/ACC/HFSA	2022 <sup>11</sup>
Management of arrhythmias in pregnancy	HRS	2023 <sup>12</sup>

\*The full-text AF guideline is from 2014.<sup>2</sup> A focused update was published in 2019.<sup>1</sup>

AATS indicates American Association for Thoracic Surgery; ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; ASA, American Stroke Association; ASE, American Society of Echocardiography; CCS, Canadian Cardiovascular Society; CHEST, American College of Chest Physicians; EACTS, European Association for Cardio Thoracic Surgery; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; HFSA, Heart Failure Society of America; HRS, Heart Rhythm Society; SAEM, Society for Academic Emergency Medicine; SCAI, Society for Cardiovascular Angiography and Interventions; SCCT, Society of Cardiovascular Computed Tomography; SCMR, Society for Cardiovascular Magnetic Resonance; and STS, Society of Thoracic Surgery.

### 1.4. Scope of the Guideline

In developing the "2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation" (2023 atrial fibrillation guideline), the writing committee reviewed previously published guidelines. Table 1 contains a list of these publications deemed pertinent to this writing effort and is intended for use as a resource, thus obviating the need to repeat existing guideline recommendations.

### 1.5. Class of Recommendations and Level of Evidence

The Class of Recommendation (COR) indicates the strength of recommendation and encompasses 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 2).

**Table 2. Applying American College of Cardiology/American Heart Association Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care\* (Updated May 2019)**

CLASS (STRENGTH) OF RECOMMENDATION	LEVEL (QUALITY) OF EVIDENCE‡
<b>CLASS 1 (STRONG)</b> <span style="float: right;"><b>Benefit &gt;&gt;&gt; Risk</b></span> <b>Suggested phrases for writing recommendations:</b> <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 2a (MODERATE)</b> <span style="float: right;"><b>Benefit &gt;&gt; Risk</b></span> <b>Suggested phrases for writing recommendations:</b> <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 2b (WEAK)</b> <span style="float: right;"><b>Benefit ≥ Risk</b></span> <b>Suggested phrases for writing recommendations:</b> <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 3: No Benefit (MODERATE)</b> <span style="float: right;"><b>Benefit = Risk</b></span> <b>(Generally, LOE A or B use only)</b> <b>Suggested phrases for writing recommendations:</b> <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 3: Harm (STRONG)</b> <span style="float: right;"><b>Risk &gt; Benefit</b></span> <b>Suggested phrases for writing recommendations:</b> <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> <ul style="list-style-type: none"> <li>• Consensus of expert opinion based on clinical experience</li> </ul>

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 1 and 2a; 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.

### 1.6. Abbreviations

Abbreviation	Meaning/Phrase
ACE	angiotensin-converting enzyme
ACHD	adult congenital heart disease
ACS	acute coronary syndrome
AF	atrial fibrillation
AFL	atrial flutter
AHRE	atrial high-rate episodes
ANS	autonomic nervous system
AP	accessory pathway
APT	antiplatelet therapy

Abbreviation	Meaning/Phrase
ARB	angiotensin receptor blocker
AT	atrial tachycardia
AVNA	atrioventricular nodal ablation
BiVP	biventricular pacing
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BTK	Bruton's tyrosine kinase
CABG	coronary artery bypass graft surgery
CAD	coronary artery disease
CCD	chronic coronary disease

(Continued)

Abbreviation	Meaning/Phrase
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
CHD	congenital heart disease
CHF	congestive heart failure
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
COR	Class of Recommendation
CrCl	creatinine clearance
CRT	cardiac resynchronization therapy
CTI	cavotricuspid isthmus
CVD	cardiovascular disease
DAT	dual antithrombotic therapy
DOAC	direct oral anticoagulant
ECG	electrocardiogram
EF	ejection fraction
eGFR	estimated glomerular filtration rate
FDA	US Food and Drug Administration
GDMT	guideline-directed management and therapy
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HR	hazard ratio
ICD	implantable cardioverter-defibrillator
ICH	intracranial hemorrhage
LA	left atrium
LAA	left atrial appendage
LAAO	left atrial appendage occlusion
LOE	Level of Evidence
LRFM	lifestyle risk factor modification
LV	left ventricular
LVEF	left ventricular ejection fraction
MI	myocardial infarction
MRA	mineralocorticoid receptor antagonist
NYHA	New York Heart Association
OAC	oral anticoagulant
PAC	premature atrial contraction
PAD	peripheral artery disease
PCI	percutaneous coronary intervention
PCC	prothrombin complex concentrate
PE	pulmonary embolism
PH	pulmonary hypertension
PH <sub>PVD</sub>	pulmonary hypertension with pulmonary vascular disease

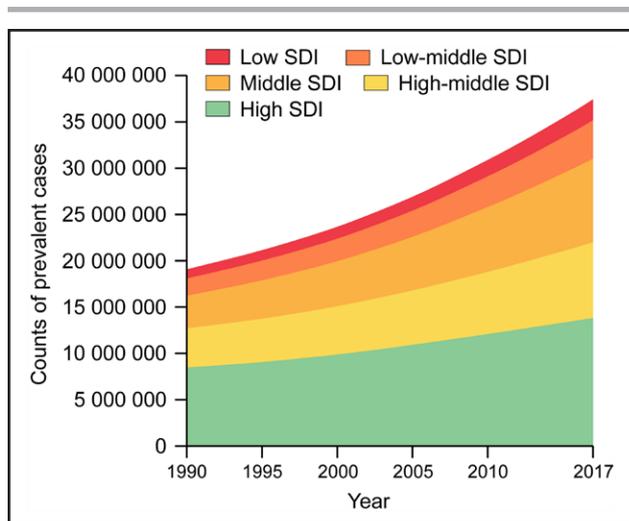
Abbreviation	Meaning/Phrase
PITP	pill-in-the-pocket
pLAAO	percutaneous left atrial appendage occlusion
PV	pulmonary veins
PVI	pulmonary vein isolation
QOL	quality of life
RAAS	renin-angiotensin-aldosterone system
RCT	randomized controlled trial
RV	right ventricular
RVP	right ventricular pacing
SDB	sleep-disordered breathing
SDOH	social determinants of health
SDM	shared decision-making
S-LAAO	surgical removal of the left atrial appendage occlusion
SVT	supraventricular tachycardia
TEE	transesophageal echocardiogram
TIA	transient ischemic attack
UREG	underrepresented racial and ethnic groups
VF	ventricular fibrillation
VHD	valvular heart disease
VKA	vitamin K antagonist
VT	ventricular tachycardia
WPW	Wolff-Parkinson-White

## 2. BACKGROUND AND PATHOPHYSIOLOGY

### 2.1. Epidemiology

Atrial fibrillation (AF) is the most sustained common arrhythmia, and its incidence and prevalence are increasing in the United States and globally (Figures 1 to 3).<sup>1,2</sup> The increasing burden is multifactorial; causes include the aging of the population, rising tide of obesity, increasing detection, and increasing survival with AF and other forms of cardiovascular disease (CVD). The estimated global prevalence was 50 million in 2020.<sup>2,3</sup> Although the prevalence of undiagnosed AF in the community is unknown, using back-calculation methodology, investigators have estimated that, in 2015, about 11% (591 000 cases) of the >5.6 million AF cases in the United States were undiagnosed.<sup>4</sup>

AF is associated with higher health care utilization and costs.<sup>2</sup> Using US data from Optum (an administrative claims database for commercially insured [United Healthcare] patients in the United States), compared with patients without AF, patients with incident AF had an increased risk of inpatient visits and more cardiovascular-related emergency department visits (relative risk [RR], 2.41 [95% CI, 2.35–2.47]).<sup>5</sup> AF is costly. Examining Optum data, individuals with AF have annual health care



**Figure 1. Temporal Trends in Counts and Age-Standardized Rates of AF-Prevalent Cases by Social Demographic Index Quintile for Both Sexes Combined, 1990–2017.**

Trends in counts of AF-prevalent cases by SDI quintile, 1990–2017. SDI was made up of the geometric mean of 3 common indicators: the lag distributed income per capita, mean educational achievement for those aged  $\geq 15$  y, and total fertility rate  $< 25$  y. SDI ranged from 0 to 1, where 0 represents the theoretical minimum level of development, whereas 1 represents the theoretical maximum level of development. Modified from Dai et al<sup>7</sup> by permission of Oxford University Press on behalf of the European Society of Cardiology. Copyright 2020 Oxford University Press. AF indicates atrial fibrillation; and SDI, Social Demographic Index.

costs of \$63 031, which is \$27 896 more than individuals without AF.<sup>5</sup> Investigators examining public and private health insurer data estimated that in US dollars in 2016, AF accounted for \$28.4 billion (95% CI, \$24.6 billion–\$33.8 billion) in health care spending.<sup>6</sup>

### 2.1.1. Prevalence, Incidence, Morbidity, and Mortality

AF prevalence in the United States was estimated to be 5.2 million in 2010, with an expectation to rise to 12.1 million in 2030.<sup>1</sup> Corresponding estimates for US incidence was 1.2 million cases in 2010, with an expectation to rise to 2.6 million cases in 2030.<sup>1</sup> The rate of AF diagnosis varies by education, income,<sup>2</sup> clinical,<sup>3,4</sup> and genetic<sup>3</sup> factors. Overall lifetime risk is about 30% to 40% in White individuals,<sup>2–4</sup> about 20% in African American individuals,<sup>2</sup> and about 15% in Chinese<sup>5</sup> individuals.

AF is associated with a 1.5- to 2-fold increased risk of death<sup>6,7</sup>; studies suggest that the mortality risk may be higher in women than in men.<sup>6</sup> In meta-analyses, AF is also associated with increased risk of multiple adverse outcomes, including a 2.4-fold risk of stroke,<sup>7</sup> 1.5-fold risk of cognitive impairment or dementia,<sup>8</sup> 1.5-fold risk of myocardial infarction (MI),<sup>9</sup> 2-fold risk of sudden cardiac death,<sup>10</sup> 5-fold risk of heart failure (HF),<sup>7</sup> 1.6-fold risk of chronic kidney disease (CKD),<sup>7</sup>

and 1.3-fold risk of peripheral artery disease (PAD).<sup>7</sup> In Medicare beneficiaries, the most frequent outcome in the 5 years after AF diagnosis was death (19.5% at 1 year; 48.8% at 5 years)<sup>11</sup>; the next most common diagnosis was HF (13.7%), followed by new-onset stroke (7.1%), gastrointestinal hemorrhage (5.7%), and MI (3.9%).<sup>11</sup>

### 2.1.2. Risk Factors and Associated Heart Disease

In Table 3, we present the evidence for the most widely reported and validated factors for AF from single studies, meta-analyses, and Mendelian randomization studies. Risk factors include demographic, anthropometric, and cardiovascular risk factors, CVD, noncardiac conditions, biomarkers (eg, electrocardiographic, imaging, circulating), and genetic markers.<sup>1</sup> Models predicting risk of AF onset are presented in **Section 4.1 (“Risk Stratification and Population Screening”)**. Most studies of AF risk factors and outcomes have been reported from high-income countries and in individuals of European ancestry.

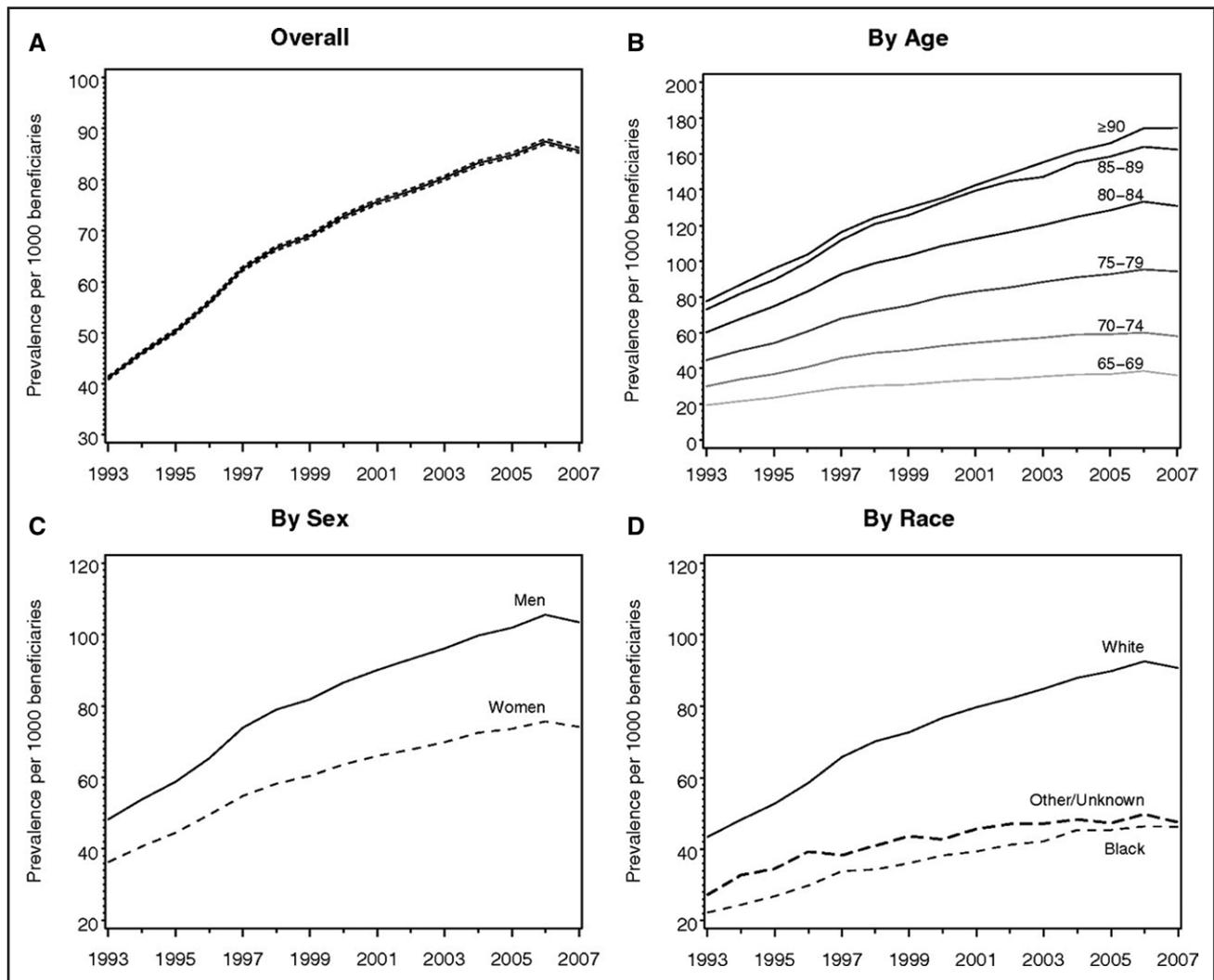
## 2.2. Atrial Arrhythmia Classification and Definitions

### 2.2.1. AF Classification

The previous classification of AF, which was based only on arrhythmia duration, although useful, tended to emphasize AF once it was diagnosed and focused mainly on therapeutic interventions. The new proposed classification using stages aims to correct the deficiencies of the previous classification by recognizing AF as a progressive disease that requires different strategies at the different stages, from prevention to screening, to rate and rhythm control therapies. The different stages better define AF as a progressive disease and highlight the need to address it at the earliest stages, especially emphasizing the importance of prevention, risk factor management, and timing for screening in those patients at the highest risk. The stages are not mutually exclusive (eg, risk factors should be managed through multiple stages) (Figure 4).

AF is the most common arrhythmia in the world and accounts for significant morbidity and mortality. Over the past decade, evidence has consistently shown that the best treatment of atrial fibrillation requires multiple stakeholders committed to providing comprehensive patient-centered care. In addition, as emphasized in this guideline, AF should be thought of in a more holistic sense over an individual patient's lifetime.

The foundation of optimal AF management is the treatment of risk factors and implementing lifestyle changes to decrease the likelihood of developing AF (Figure 5). Once AF develops, patient care should focus on assessing the risk of stroke and implementing any necessary treatment, continued optimization of all modifiable risk factors, and



**Figure 2. Prevalence of AF Among Medicare Beneficiaries, 1993–2007.**

(A) In the overall cohort, (B) by age group, (C) by sex, and (D) by race. The dashed lines in panel A represent 95% CIs. Reproduced with permission from Piccini et al.<sup>8</sup> Copyright 2012 American Heart Association, Inc. AF indicates atrial fibrillation.

managing potential symptoms of AF, with an initial focus on evaluating and minimizing AF burden. However, as outlined in this guideline, access to all aspects of health care to all patients is necessary for any true improvement to be realized.

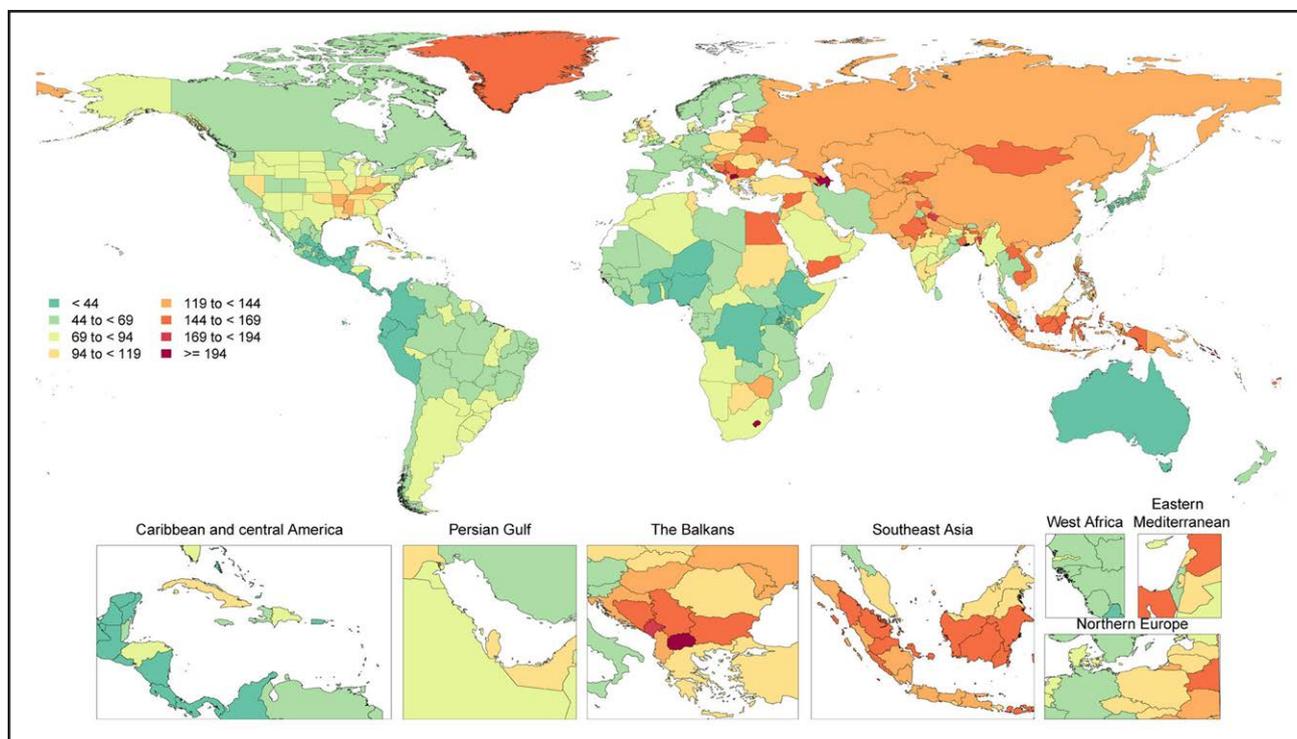
When AF develops, holistic and optimal care of the patient at risk for AF, or who has developed AF, can be simply modeled using a building. The foundation of care is treatment of comorbidities and risk factors and implementing behavioral change in all individuals to decrease the likelihood of developing AF and reducing its burden (Screening for all risk factors from **HEAD 2 TOES**). Once AF develops, there are 3 important care processes that must be specifically addressed with all patients and aligned with their goals of therapy: **S**troke risk assessment and treatment, if appropriate, **O**ptimizing all modifiable risk factors, and **S**ymptom management using rate- and rhythm-control strategies

that consider AF burden in the context of an individual patient's needs (**SOS**). The overarching principle for AF management is **Access to All Aspects of care to All (4 As)**.

### 2.2.2. Associated Arrhythmias

Other atrial arrhythmias are often encountered in patients with AF.

**Atrial Tachycardia (AT):** It is a regular atrial rhythm at a constant rate of >100 beats per minute (bpm) with discrete P waves and atrial activation sequences originating outside of the sinus node.<sup>1</sup> The mechanism can be automaticity, triggered activity, or a microreentry circuit. Focal ATs arise from a single discrete site within the left or right atrium, in contrast to macroreentrant atrial arrhythmias and AF, which involve multiple sites or larger circuits. In multifocal AT, the atrial activation sequence and P-wave morphology vary.



**Figure 3. Age-Standardized Global Prevalence Rates of AF and Atrial Flutter per 100 000, Both Sexes, 2020.**

During each annual GBD Study cycle, population health estimates are produced for the full-time series. Improvements in statistical and geospatial modeling methods and the addition of new data sources may lead to changes in past results across GBD Study cycles.

Modified with permission from Tsao et al.<sup>2</sup> Copyright 2023 American Heart Association, Inc. Source: Institute for Health Metrics Evaluation. Used with permission. All rights reserved. AF indicates atrial fibrillation; and GBD, Global Burden of Disease.

**Atrial Flutter (AFL) and Macroreentrant AT:** They occur in many of the same situations as AF. Typical AFL, also known as “typical AFL” or “cavotricuspid isthmus (CTI)-dependent AFL,”<sup>2</sup> involves a macroreentrant circuit around the tricuspid annulus traversing the CTI on the right side of the heart (Figure 6). This is the arrhythmia associated with the classic electrocardiogram (ECG) finding of sawtooth flutter waves in the inferior leads when the circuit goes in the counterclockwise direction. The same circuit in the clockwise direction is called “reverse typical AFL.” If the flutter involves a different circuit than tricuspid valve/isthmus, then it is called “atypical” AFL, which is also known as “noncavotricuspid isthmus-dependent macroreentrant AT.”<sup>2</sup> AFL was previously classified as either type I or type II. That terminology is no longer used.

### 2.3. Mechanisms and Pathophysiology

AF is a chaotic, rapid (300–500 bpm), and irregular atrial rhythm. Although normal rhythms are conducted through the atria in smooth waves initiated by the sinoatrial node, AF is the result of either electrophysiological abnormalities that underlie impulse generation and/or structural abnormalities of cellular connections that typically facilitate rapid and uniform

impulse conduction. AF often stems from waves of electrical activity originating from ectopic action potentials most commonly generated in the pulmonary veins (PVs) of the left atrium (LA),<sup>1</sup> or in response to reentrant activity promoted by heterogeneous conduction due to interstitial fibrosis.<sup>2</sup> Atrial ectopy can generate runs of tachycardia, while persistent AF requires a substrate that is either sufficiently large or conduction that is sufficiently heterogeneous to enable reentrant activity to persist. The electrical abnormalities evident on the ECG during AF likely represent a shared phenotype of a condition with many distinct etiologies (genetic, environmental, and metabolic) (Figure 7).

#### 2.3.1. Electrophysiological Mechanisms and Electrical Remodeling

The observation by Haissaguerre et al<sup>1</sup> that ectopic firing from PVs triggers AF revolutionized treatments for AF. PV features that increase vulnerability for initiating ectopy include a higher resting membrane potential, stretch-activated channels,<sup>2</sup> and pattern of cross myofiber orientation.

Electrical remodeling, which can contribute to and result from AF, includes perturbations that culminate in abnormal Ca<sup>2+</sup> handling and shortened, proarrhythmic triangulated action potentials (eg, from decreased

**Table 3. Risk Factors for Diagnosed AF**

Condition	Study Type	Effect on Risk of AF	Summary Risk of Incident AF	Effect of LRFM
<b>Risk Factors</b>				
Advancing age	SR/MA	Age per 5 y: ↑ risk (HR, 1.43-1.66) <sup>2,3</sup>	↑ Risk	N/A
	MR	Accelerated epigenetic age by MR: no association <sup>4</sup>		
Smoking	Single study	Current smoking: ↑ risk (9.8%) <sup>5</sup>	↑ Risk	N/A
	SR/MA	Smoking: ↑ risk (HR, 1.21-1.43) <sup>2,6</sup>		
	MR	Smoking initiation: ↑ risk (OR, 1.11) <sup>7</sup>		
Physical activity	SR/MA	Sedentary lifestyle: ↑ risk (OR, 2.47) <sup>8</sup> Guideline-recommended physical activity: ↓ risk (HR, 0.94) <sup>9</sup> Elite athletes vs nonathletes: ↑ risk (OR, 2.46) <sup>10</sup>	U curve: Sedentary lifestyle and elite/extreme exercise: ↑ risk	Exercise: ↓ AF burden, recurrence, symptoms; ↑ quality of life, functional capacity <sup>11-16</sup>
Alcohol	Single studies	Risk of AF episode within 4 h of 1 drink: ↑ risk (OR, 2.02) <sup>17</sup> Greater access to alcohol law: ↑ risk <sup>18</sup>	↑ Risk	Randomized abstinence: ↓ AF recurrence and burden <sup>19</sup> N-of-1 studies of alcohol avoidance: ↓ near-term AF <sup>20</sup> Alcohol avoidance or reduction as part of a comprehensive LRFM program: ↓ AF burden, symptoms, progression of AF <sup>21-24</sup>
	SR/MA	Dose response (#drinks/d): ↑ risk (RR) 1: 1.08; 2: 1.17; 3: 1.33; 4: 1.36; 5: 1.47 <sup>25</sup>		
	MR	Genetically predicted heavy alcohol consumption (>35 U/wk for women and >50 U/wk for men): ↑ risk (OR, 1.11) <sup>7</sup>		
Adiposity markers: weight, BMI, obesity	Single study	Obesity: population attributable fraction 12.7%-16.9% <sup>5,26</sup>	↑ Risk	Weight loss in overweight or obese patients with AF as part of a comprehensive LRFM program: ↓ AF symptoms, burden, recurrence, progression <sup>21-24</sup> Bariatric surgery in class III obesity: associated with reversal of AF type, ↑ sinus rhythm postablation <sup>27-29</sup> Weight loss in long-lasting persistent AF and obesity: ↔ <sup>30</sup>
	SR/MA	BMI: RR, 1.28 per 5-unit ↑ in BMI <sup>31</sup> Weight: <sup>2</sup> HR, 1.12 per 15 kg ↑		
	MR	Obesity <sup>3</sup> Birthweight: 1.26 per SD ↑ <sup>32</sup> Childhood BMI (OR, 1.18) <sup>32</sup> BMI 1.31 per unit BMI <sup>33</sup>		
Height	MA	Height per 10 cm: ↑ risk (HR, 1.28) <sup>2</sup>	↑ Risk	N/A
	SR/MA	Increasing height: ↑ risk <sup>3</sup>		
	MR	Increasing height: ↑ risk (OR per unit, 1.33) <sup>33</sup>		
Hypertension and BP	Single studies	Elevated BP: ↑ risk, population attributable fraction, 21.6% <sup>5</sup> Presence of hypertension treatment: ↑ risk (HR, 1.35-1.68), incidence 9.8%-19.5%; both AF and SBP decreased over time <sup>26</sup>	Hypertension: ↑ risk SBP: ↑ risk DBP: ↑↔ risk	Renal denervation: ↓ AF postablation <sup>34</sup> Mineralocorticoid receptor antagonists: ↓ AF burden <sup>35</sup> BP control postablation: ↔ <sup>36</sup> Intensive BP control to SBP <120 mm Hg in patients with hypertension at high risk for CVD: ↓ AF risk <sup>37</sup> BP control as part of a comprehensive LRFM program: ↓ AF burden <sup>21-24,38</sup>
	MA	BP: SBP: ↑ risk (HR per 20 mm Hg, 1.22); DBP per 10 mm Hg ↓ risk (HR, 0.90); use of BP medications ↑ risk (HR, 1.42) <sup>2</sup>		
	SR/MA	Hypertension: ↑ risk <sup>3</sup>		
	MR	SBP <sup>33,39</sup> ↑ risk; DBP mixed results ↔ risk <sup>39,40</sup> ; pulse pressure ↑ risk <sup>40</sup>		
Resting heart rate	SR/MA	Resting heart rate: J-shaped relationship with incident AF. Lowest risk at 68-80 bpm; <70 bpm (RR, 1.09 per 10 bpm ↓); >70 bpm (RR, per 10 bpm ↑ RR 1.06) <sup>41</sup>	Slow heart rate: ↑↓ variable risk	N/A
	MR	Heart rate: <65 bpm slower (HR ↑ risk); heart rate per 5 bpm ↑, 0.82 <sup>42</sup>	Higher heart rate: ↑↓ variable risk	

(Continued)

**Table 3. Continued**

Condition	Study Type	Effect on Risk of AF	Summary Risk of Incident AF	Effect of LRFM
Diabetes	Single study	Diabetes: ↑ risk, population attributable fraction 3.1% <sup>5</sup> Diabetes: ↑ risk, population attributable fraction ↑ over time 3.2%-5.9% <sup>26</sup>	↑ Risk	Optimal glycemic control preablation may ↓ AF recurrence postablation <sup>43</sup>
	MA	Diabetes: ↑ risk (HR, 1.27 [95% CI, 1.10-1.46]) <sup>2</sup>		
	SR/MA	Diabetes: ↑ risk (RR, 1.28, excluding large outlying study) <sup>44</sup> Pre-diabetes: ↑ risk (RR, 1.20) <sup>44</sup> Blood glucose; ↑ risk (RR per 20 mg/dL ↑, 1.11) <sup>44</sup>		
<b>Cardiovascular disease</b>				
HF or CAD	Single study	HF or CAD: population attributable fraction 5.4% <sup>5</sup>	↑ Risk	N/A
HF	Single studies	HF: ↑ risk but population attributable fraction ↓ d over time 7.8%-1.4% <sup>26</sup> Bidirectional relation between AF and HF <sup>45</sup>	↑ Risk	N/A
	MA	History of HF: ↑ risk (HR, 2.02) <sup>2</sup>		
	MR	Genetically predicted HF: ↑ risk (OR, 1.86) <sup>46</sup>		
CAD	Single study	MI: Population attributable fraction 3.6% <sup>26</sup>	↑ Risk	N/A
	MA	History of MI: HR, 1.64 <sup>2</sup>		
	MR	Genetically predicted CAD: OR, 1.18 <sup>33</sup>		
VHD	Single studies	Significant heart murmur: ↑ risk (HR, 2.38) <sup>47</sup> Significant heart murmur (any diastolic and grade ≥3/6 systolic murmur): ↑ risk, population attributable fraction 21.9% ↓ d over time to 3.1% <sup>26</sup>	↑ Risk	N/A
	MR	Genetically predicted risk of AF in individuals of European ancestry: associated with VHD with rheumatic fever (OR, 1.26) and nonrheumatic VHD (OR, 1.27) <sup>48</sup>		
Cardiac surgery	Single study	Multicenter validated risk prediction model: ↑ risk AF after CABG <sup>49</sup>	↑ Risk	Prophylactic amiodarone, beta blockers: ↓↔ postop AF <sup>50-54</sup> Posterior left pericardiotomy during CABG, aortic valve, ascending aortic aneurysm surgery: ↓ postop AF <sup>55,56</sup>
	SR/MA	Postop AF incidence: 23.7%-25.5% <sup>56</sup> of cardiac surgery patients <sup>57</sup>		
<b>Other conditions</b>				
CKD	SR/MA	CKD: ↑ risk (HR, 1.47) <sup>58</sup>	↑↔ Risk	N/A
	MR	Bidirectional relation between CKD and AF <sup>59</sup> AF causal for CKD; CKD not causal for AF <sup>60</sup>		
Obstructive sleep apnea	SR/MA	OSA: ↑ risk (OR, 1.71), with potential dose response relation by severity <sup>61</sup>	↑ Risk	Observational studies of SDB treatment: ↓ AF burden <sup>62-67</sup> Small RCTs of SDB treatment: ↔ <sup>68-70</sup>
	MR	Genetically predicted OSA: ↑ risk (OR, 1.21) <sup>71</sup>		
Thyroid disease	SR/MA	Clinical hyperthyroidism: ↑ risk (RR, 2.35) <sup>72</sup>	↑ Risk	
	MR	Hyperthyroidism: ↑ risk (OR, 1.31) <sup>73</sup>		
Sepsis	Single study	Severe sepsis: ↑ risk (OR, 6.82) <sup>74</sup> ; Medicare population <sup>75</sup>	↑ Risk	N/A
	SR/MA	Sepsis severity: ↑ risk <sup>76</sup>		

(Continued)

**Table 3. Continued**

Condition	Study Type	Effect on Risk of AF	Summary Risk of Incident AF	Effect of LRFM
<b>Markers on ECG</b>				
PR interval	SR/MA	Prolonged PR: ↑ risk (RR, 1.45) <sup>77</sup>	Prolonged PR: ↑ risk PR interval polygenic risk score: ↓ risk PR interval risk SNPs: variable ↑↓ risk	N/A
	MR	Polygenic risk score PR interval prolongation: ↓ AF risk (OR, 0.95; $P=4.30 \times 10^{-8}$ ) with some variants associated with ↑ and some with ↓ AF risk <sup>78</sup>		
LVH	Single study	ECG LVH: Population attributable fraction 10.4% ↓ d over time to 1.8% <sup>26</sup>	↑ Risk	N/A
	SR/MA	LVH: ↑ risk (RR, 1.46) <sup>79</sup>		
<b>Biomarkers</b>				
Natriuretic peptides	MA	BNP: ↑ risk (HR per 1-SD ln-BNP, 1.66) <sup>80</sup>	↔ Risk	N/A
	MR	Natriuretic peptides not associated <sup>81</sup>		
Inflammatory markers	SR/MA	CRP: ↑ risk (SMD, 0.95) <sup>82</sup> IL-6: ↑ risk (SMD, 0.89) <sup>82</sup> TNF-α: ↑ risk (SMD, 2.20) <sup>82</sup>	CRP, IL-6, TNF-α, DUSP13, FKBP7, Spondin-1: ↑ risk IL-6R, TNFS12: ↓ risk	N/A
	MR	DUSP13, FKBP7, Spondin-1 ↑ risk <sup>33</sup> IL-6R, TNFS12 ↓ risk <sup>33</sup>		
Lp(a)	SR/MA	Lp(a): HR, 1.03; only 39% of Lp(a) risk mediated via ASCVD <sup>83</sup>	↑ Risk	N/A
	MR	Genetically predicted ↑ Lp(a): ↑ risk (HR per 23 mg/dL genetically predicted ↑ Lp(a), 1.04) <sup>83</sup>		
<b>Imaging markers</b>				
LA size or function	Single studies	LA anterior-posterior dimension: ↑ risk (HR per 5 mm ↑, 1.39) <sup>84</sup> End diastolic LA volume (min): ↑ risk (HR, 1.12) <sup>85</sup> LA emptying fraction: ↑ risk (HR, 1.03) <sup>85</sup>	↑ LA size, emptying fraction: ↑ risk	Surgical LA reduction in conjunction with cardiac surgery or surgical AF ablation in patients with persistent AF may ↑ rates of sinus rhythm <sup>86-89</sup>
	MR	Genetic susceptibility to AF (independent measure) is associated with ↑ indexed LA size and ↓ LA ejection fraction (dependent measures) <sup>90</sup>		
LV wall thickness	Single study	LV posterior wall thickness: ↑ risk (HR per 4-mm ↑, 1.28) <sup>84</sup>	↑ Risk	N/A
	SR/MA	LVH: ↑ risk (RR, 1.46) <sup>79</sup>		
<b>Social determinants of health</b>				
Education	Single studies	Higher education: ↑ lifetime risk of AF (US-based ARIC study) <sup>91</sup> Higher education in young individuals: ↓ risk of AF diagnosis (Danish study) <sup>92</sup>	Variable ↑↓ risk	N/A
	MR	AF risk related but largely mediated via BMI (57.5%), type 2 diabetes (9.8%), SBP (18.7%), and smoking (7.1%) <sup>93</sup>		
Income	Single studies	Higher income: ↑ lifetime risk of AF (US-based ARIC study) <sup>91</sup> Higher income in young individuals: ↓ risk of AF diagnosis (Danish study) <sup>92</sup>	Variable ↑↓ risk	N/A

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**Table 3. Continued**

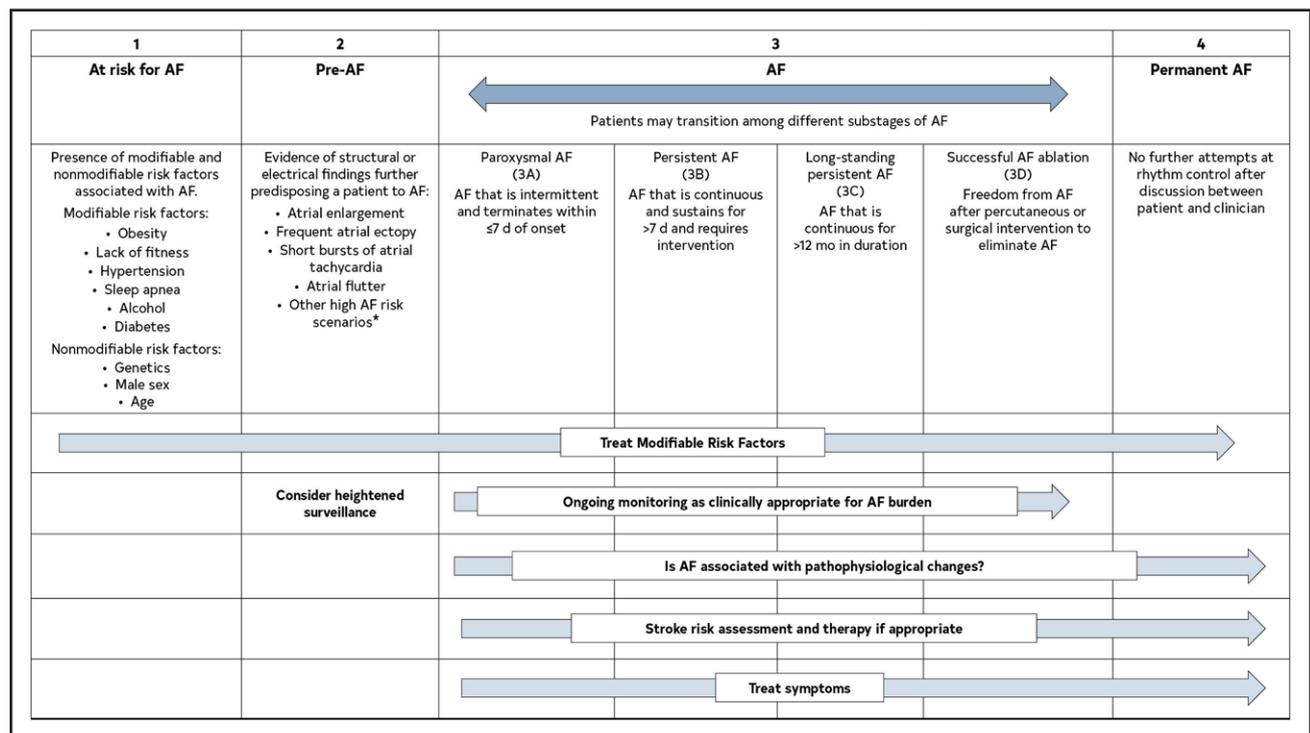
Condition	Study Type	Effect on Risk of AF	Summary Risk of Incident AF	Effect of LRFM
SES	Single studies	Cumulative socioeconomic disadvantage: ↑ risk (HR, 1.57) <sup>94</sup> Individual's poorest areas: 12% ↑ d risk <sup>95</sup>	Low SES: ↑↔ risk	N/A
	SR/MA	Heterogeneous results <sup>96</sup>		
<b>Genetics</b>				
Family history/ heritability	Single studies	Family history of AF: ↑ risk <sup>97-99</sup>	↑ Risk	N/A
	MR	Proportion heritability explained by loci in European ancestry analysis, 42% <sup>100</sup>		
GWAS	MA	Number of AF risk loci ↑s with ↑ number of subjects studied. In 2018, 97-111 loci explained ~11%-42% of the heritability of AF in individuals of European ancestry <sup>100,101</sup>	↑ Risk	N/A

Population attributable fraction: the proportional disease incidence in the population that is estimated to be due to the risk factor. Statistically significant associations reported, unless otherwise indicated.

↓ indicates decreased; ↑, increased; ↔ no significant change in risk; AF, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; ECG, electrocardiogram; GWAS, genome-wide association study; HF, heart failure; HR, hazard ratio; LA, left atrial; LRFM, lifestyle and risk factor modification; LV, left ventricular; LVH, left ventricular hypertrophy; MA, meta-analysis; MR, Mendelian randomization; N/A, not available/applicable; OR, odds ratio; RR, relative risk; OSA, obstructive sleep apnea; SMD, standardized mean difference; SBP, systolic blood pressure; SES, socioeconomic status; SR, systematic review; and VHD, valvular heart disease.

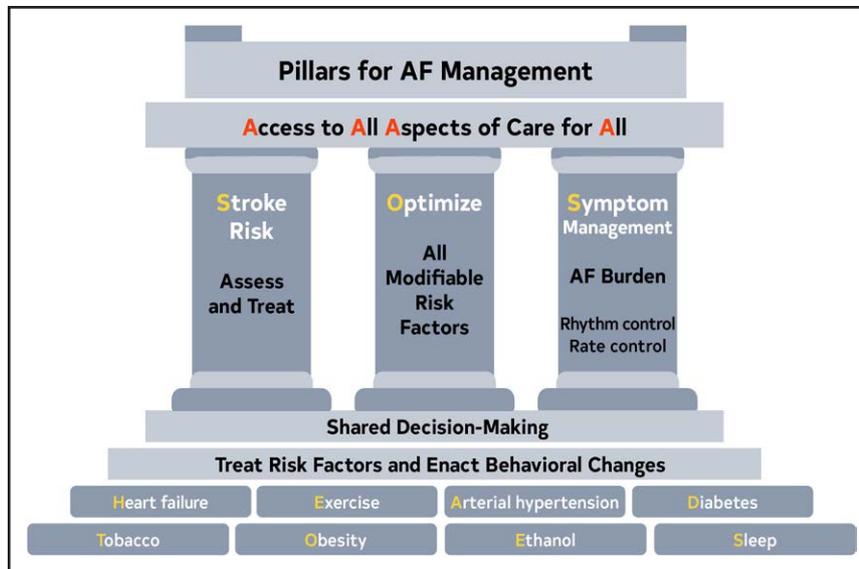
L-type Ca<sup>2+</sup> current<sup>3</sup> and increase in I<sub>K1</sub>).<sup>4</sup> Heterogeneity in I<sub>K1</sub> between left and right atria further promotes arrhythmogenicity.<sup>5</sup> Downregulation of connexin results in decreased gap junctions, leading to slow heterogeneous atrial conduction velocity and repolarization,<sup>6</sup>

promoting regional functional conduction block that can support reentry. Connexin remodeling can be due to genetic<sup>7</sup> or acquired factors, such as inflammatory state,<sup>8,9</sup> older age, or sleep-disordered breathing (SDB).<sup>10</sup>



**Figure 4. AF Stages: Evolution of Atrial Arrhythmia Progression.**

\*Heart failure, valve disease, coronary artery disease, hypertrophic cardiomyopathy, neuromuscular disorders, thyroid disease. Original figure created by the 2023 Atrial Fibrillation Guideline Writing Committee. AF indicates atrial fibrillation.



**Figure 5. Pillars for AF Management.**  
AF indicates atrial fibrillation.

Calcium mishandling from remodeling increases calcium load in the sarcoplasmic reticulum and dysfunction of ryanodine receptors, which regulate intracellular calcium release. Remodeling in AF of sarcoplasmic reticulum calcium ATPase underlies sequestration of intracellular calcium between beats, and/or altered regulation of sarcoplasmic reticulum calcium ATPase by phospholamban and sarcolipin.<sup>11</sup> Increased intracellular sodium from calcium-calmodulin II-induced increased late sodium current or cardiac glycosides can also increase sarcoplasmic reticulum calcium through the sodium-calcium exchanger.<sup>12,13</sup> Several upstream mechanisms (eg, oxidative stress, inflammatory signaling) promote calcium-calmodulin II -activation. CaMKII-mediated and hyperphosphorylation of ryanodine receptor 2 promotes spontaneous diastolic  $\text{Ca}^{2+}$  leak by increasing ryanodine receptor 2 channel open probability, leading to higher intracellular  $\text{Ca}^{2+}$  levels and the milieu for delayed afterdepolarizations, the most likely trigger for AF initiation.<sup>14</sup> Electrogenic action of sodium-calcium exchanger drives afterdepolarizations, and expression of sodium-calcium exchanger is increased in HF and AF. Action potential alternans related to  $\text{Ca}^{2+}$  mishandling can be noted to precede AF onset and increases with age.

### 2.3.1.1. Triggers of AF

The atria of patients with AF tend to have both shorter effective refractory periods and slower conduction, which enhances dispersion of repolarization and favor reentry. This substrate is sensitive to AF initiation, frequently after premature atrial contractions (PACs).<sup>1</sup> PAC burden is associated with development of AF.<sup>2</sup> Larger LA volume, increased NT-proBNP levels, and impaired LA emptying are associated with increased PAC burden.<sup>3</sup> In a study of 100 patients undergoing PV isolation, PACs induced 41 episodes of AF in 22 patients, with most episodes

originating in the PVs.<sup>4</sup> Earlier studies also reported an LA gradient of background potassium currents, resulting in shorter LA than right atrial effective refractory period in patients with AF.<sup>5</sup> Mapping studies of AF electrograms in canine models documented a left-right gradient of high frequency sources (drivers), with the highest frequency regions located near the PVs in the LA.<sup>6</sup>

### 2.3.2. Atrial Structural Abnormalities, Remodeling, and Atrial Myopathy

Atrial cardiomyopathy has been identified as “any complex of structural, architectural, contractile or electrophysiological changes affecting the atria with the potential to produce clinically relevant manifestations.”<sup>1</sup> Atrial cardiomyopathy is common, associated with aging and other comorbidities with metabolic or hemodynamic stress, and often leads to or results from AF. Structural and electrical remodeling promote AF and include interstitial changes, increased myofibroblast activity, and collagen deposition, fibrofatty deposits, altered ion channel expression, calcium signaling and contractility, and inflammatory infiltrates.<sup>1</sup> Myeloperoxidase, an oxidase in neutrophils and macrophages, is associated with fibroblast activation, interstitial fibrosis, and inducibility of AF in a mouse model.<sup>2</sup> Prothrombotic changes are often evident in the LA, including increased endocardial expression of von Willebrand factor, vascular cell adhesion molecule-1 and monocyte chemoattractant protein-1 changes, which may increase risk of thrombus formation and stroke.<sup>1</sup>

Experimental hemodynamic overload, such as reversible aortopulmonary artery shunting promotes atrial dilation, atrial myocyte hypertrophy, interstitial fibrosis, alterations in extracellular matrix composition and vascular dysfunction, and increased vulnerability to atrial ectopy and AF inducibility.<sup>3</sup> Electrical remodeling similar to that seen during AF is observed, with characteristic

**Table 4. Definitions**

Term	Definition
AF	A supraventricular tachyarrhythmia with uncoordinated atrial activation and ineffective atrial contraction
	Electrocardiographic characteristics include (1) irregular R-R intervals (when atrioventricular conduction is present), (2) absence of distinct P waves, and (3) irregular atrial activity also known as fibrillatory waves. AF can be documented by, for example, 12-lead ECG, rhythm strips, wearables, intracardiac electrograms, but will always require visual confirmation that the diagnosis is accurate.
Clinical AF	With the increasing availability of wearable devices and other continuous monitoring technologies, the distinction between clinical and subclinical AF has become increasingly blurred, thus the writing committee felt the term clinical AF has become less useful. Yet, the term was kept because most of the evidence from randomized trials that have led to guideline recommendations for the treatment of AF refer to "clinical AF." These trials required electrocardiographic documentation of the arrhythmia for inclusion and most patients presented for clinical evaluation and/or therapy of the arrhythmia.
Subclinical AF	Subclinical AF refers to this arrhythmia identified in individuals who do not have symptoms attributable to AF and in whom there are no previous ECGs documenting AF This includes AF identified by implanted devices (pacemakers, defibrillators, or implantable loop recorders) or wearable monitors
Atrial high-rate episodes	These are defined as atrial events exceeding the programmed detection rate limit set by the device. These are recorded by implanted devices but require visual inspection to confirm AF and exclude other atrial arrhythmias, artifact or oversensing.
AF burden	AF burden encompasses both frequency and duration and refers to the amount of AF that an individual has. AF burden has been defined differently across studies. For the purpose of this guideline, AF burden will be defined as the durations of an episode or as a percentage of AF duration during the monitoring period depending on how it was defined in the individual studies.
First detected AF	The first documentation of AF, regardless of previous symptoms
Paroxysmal AF	AF that is intermittent and terminates within $\leq 7$ d of onset
Persistent AF	AF that is continuous and sustains for $>7$ d and requires intervention. Of note, patients with persistent AF who, with therapy, become paroxysmal should still be defined as persistent as this reflects their original pattern and is more useful to predict outcomes and define substrate.
Long-standing persistent AF	AF that is continuous for $>12$ mo in duration
Permanent AF	A term that is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm Acceptance of AF represents a therapeutic decision and does not represent an inherent pathophysiological attribute of AF
<b>Terms considered obsolete</b>	
Chronic AF	This historical term has had variable definitions and should be abandoned. It has been replaced by the "paroxysmal," "persistent," "long-standing persistent," and "permanent" terminology.
Valvular and nonvalvular AF	The distinction between "valvular" and "nonvalvular" AF remains a matter of debate. Their definitions may be confusing. Recent trials comparing vitamin K antagonists with non-vitamin K antagonist oral anticoagulants in AF were performed among patients with so-called "nonvalvular" AF. These trials have all allowed native valvular heart disease other than mitral stenosis (mostly moderate and severe) and prosthetic heart valves to be included. We should no longer consider the classification of AF as "valvular" or "nonvalvular" for the purpose of defining the etiology of AF, since the term was specific for eligibility of stroke risk reduction therapies. Valvular and nonvalvular terminology should be abandoned.
Lone AF	This term has been used in the past to identify AF in younger patients without structural heart disease who are at a lower risk for thromboembolism. This term does not enhance patient care, is not currently used, and should be abandoned.

AF indicates atrial fibrillation.

loss of calcium currents. Shunt closure reverses electrophysiological changes.<sup>3</sup> Clinically, the hemodynamic structural changes are difficult or impossible to reverse.

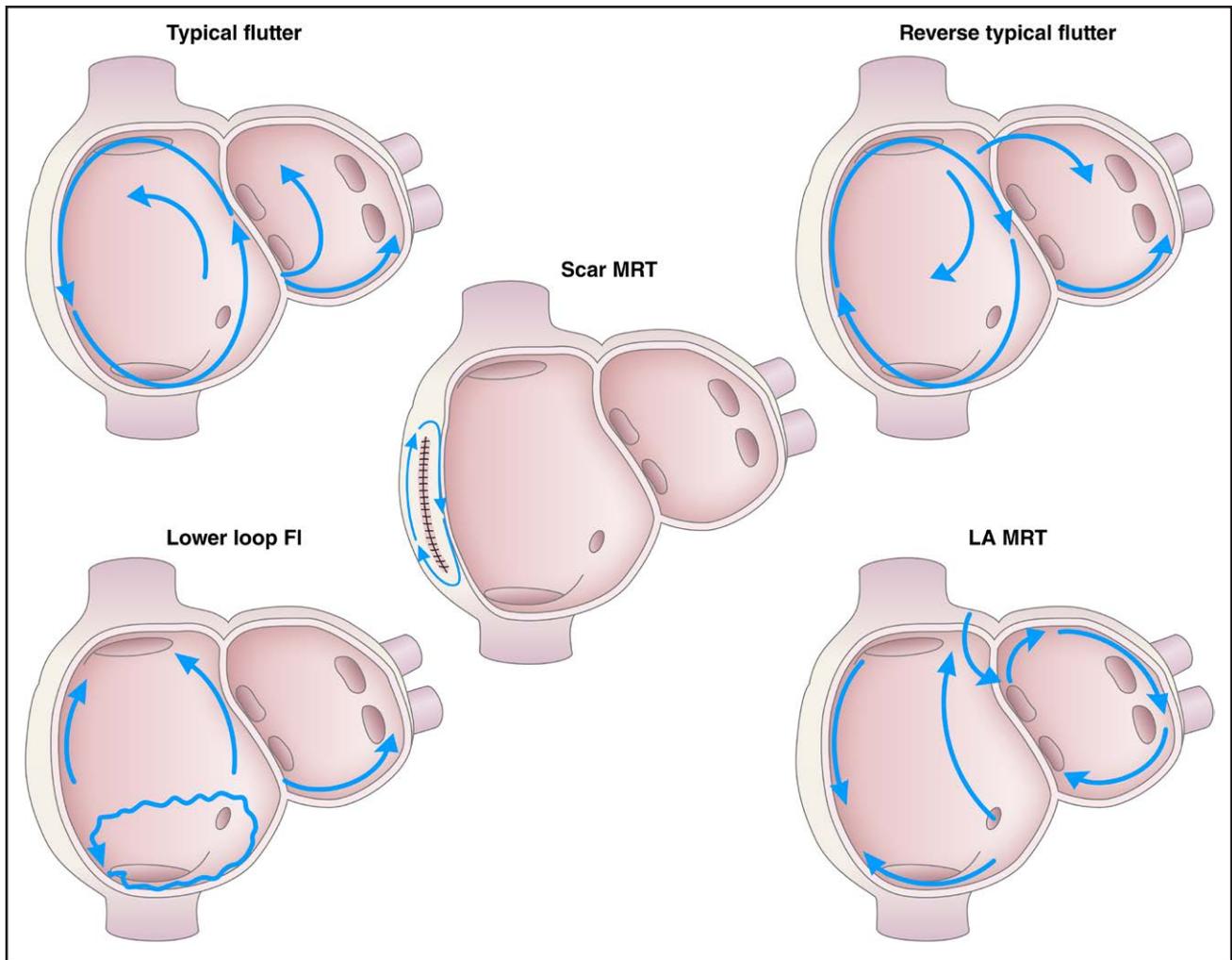
### 2.3.2.1. Upstream Pathways

Upstream pathways include inflammatory, oxidative stress, fibrosis, calcium handling, genetic, metabolic, obesity, and other mechanisms implicated in increasing susceptibility to or progression of AF. The renin-angiotensin-aldosterone system (RAAS), oxidative stress, inflammatory signaling, and calcium overload are discussed here and in **Section 2.3.1 ("Electrophysiological Mechanisms and Electrical Remodeling")**. Upstream therapies are discussed in **Section 8.3.4 ("Upstream Therapy")**.

The RAAS regulates blood pressure (BP) and is activated in hypertension and obesity. RAAS activation promotes vascular smooth muscle constriction (increasing BP), activates fibroblasts (increasing atrial intersti-

tial collagen), and increases reactive oxygen species in the sympathetic nervous system. BP and weight control, including treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers, attenuate pathologic changes.

Oxidative stress is associated with: (1) activation of calcium-dependent calmodulin kinase II<sup>1,2</sup> and jun kinase 2,<sup>3</sup> which promotes ryanodine receptor phosphorylation and leads to spontaneous calcium release<sup>4</sup>; (2) increased late sodium current,  $I_{NaL}$ , and lower calcium current amplitude; (3) formation of reactive lipid products (isolevuglandins) in hypertension<sup>5</sup> and AF<sup>6</sup>; (4) activation of the redox-sensitive transcription factor nuclear factor-kappa B and the NLRP3 inflammasome<sup>7</sup>; (5) increase in mitochondrial and metabolic stress; (6) inflammatory changes; and (7) myofilament protein degradation, impairing atrial contractility, which may increase thromboembolism risk.<sup>8</sup>



**Figure 6. Types of Atrial Flutter and Macroreentrant Atrial Tachycardia.**

The typical, reverse typical, and the lower-loop flutter all have the low right atrial isthmus incorporated in the flutter circuit. Other macroreentrant flutters include scar-mediated reentrant tachycardia and left mitral isthmus flutter. Modified with permission from Wellens et al.<sup>3</sup> Copyright 2002 American Heart Association, Inc. FI indicates flutter; LA, left atrium; and MRT, macroreentrant.

Systemic inflammatory activation, first documented with AF after cardiac surgery,<sup>9</sup> has also been associated with nonsurgical AF.<sup>10</sup> NLRP3 knockdown prevented AF inducibility in a mouse model, implicating the NLRP3 inflammasome in AF pathophysiology.<sup>11</sup> NLRP3-blockers are in development.

### 2.3.2.2. Persistence of AF

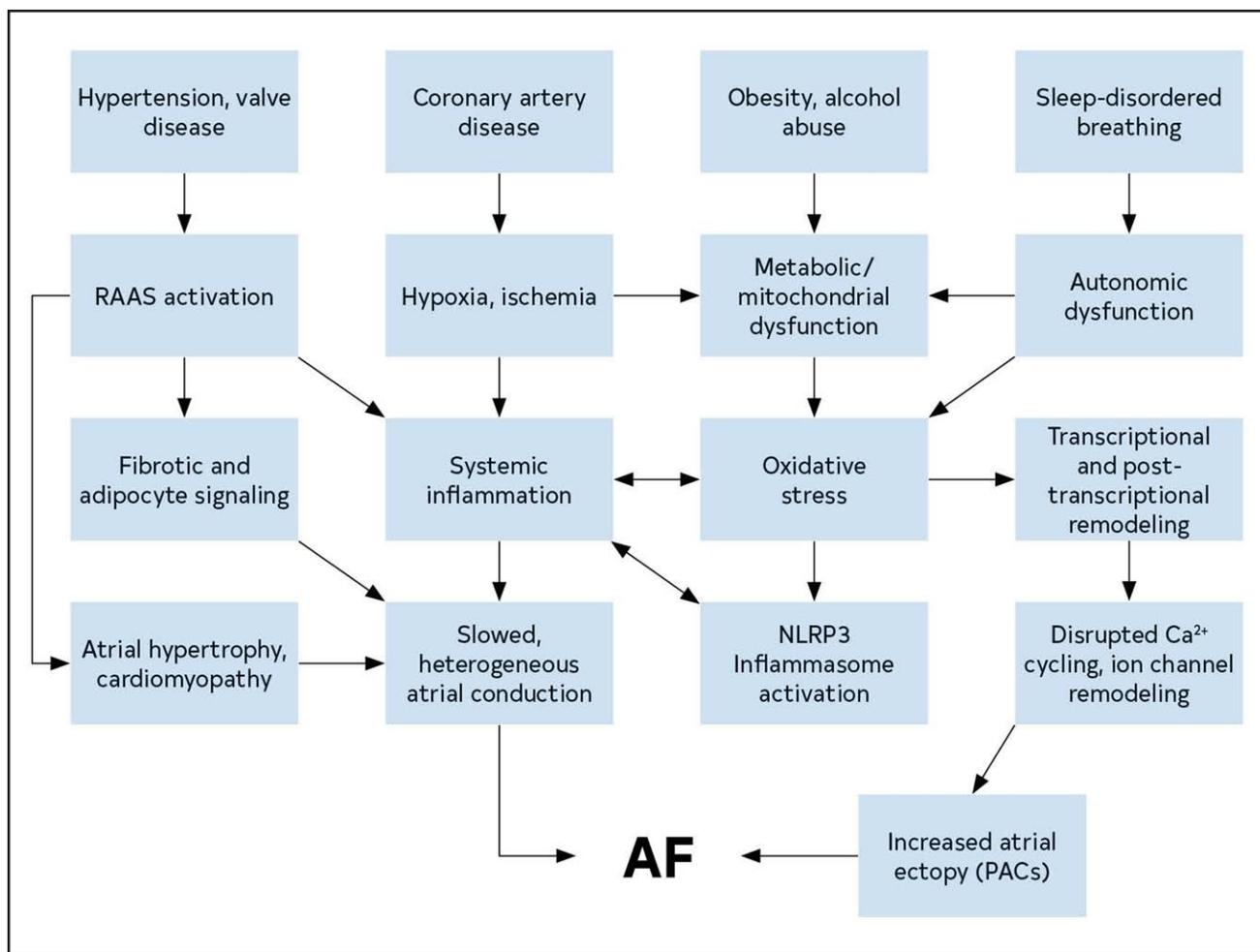
In general, persistence of AF reflects the substrate for AF. A suitable substrate for AF has a wavelength (wavelength = refractory period × conduction velocity) that is shorter than the dimensions of the tissue, with heterogeneous conduction velocity and/or repolarization duration. Thus, an individual with large, fibrotic, and/or fatty atria is more likely to have persistent AF than one with a normal-sized atria with little interstitial fibrosis or adipose infiltration. Electrophysiologic remodeling is typically a response to persistent AF rather than the trigger.

### 2.3.3. Role of the Autonomic Nervous System

The autonomic nervous system (ANS) has an important role as trigger and substrate (Figure 8).

#### ANS triggers AF

The ANS as AF trigger is detailed in several reviews.<sup>1–6</sup> Sympathetic efferent stimulation releases noradrenaline, stimulating G-coupled  $\beta$ -adrenergic receptors, enhancing L-type calcium channels, and increasing inward current (automaticity/early afterdepolarization). Delayed afterdepolarization occurs via calcium overload and ryanodine-2 receptor dysfunction. Parasympathetic stimulation shortens atrial effective refractory period by increasing  $I_{KACH}$  (acetyl-choline receptor mediated inward rectifying potassium channel) activity. Atrial effective refractory period heterogeneity follows the pattern of autonomic innervation. Sympathetic and parasympathetic activity, alone or combined, can trigger AF.



**Figure 7. Mechanisms and Pathways Leading to AF.**

The pathways that contribute to the development of AF create a substrate for reentry and provide triggers that can initiate arrhythmic activity. AF indicates atrial fibrillation; PAC, premature atrial contraction; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; and RAAS, renin-angiotensin-aldosterone system.

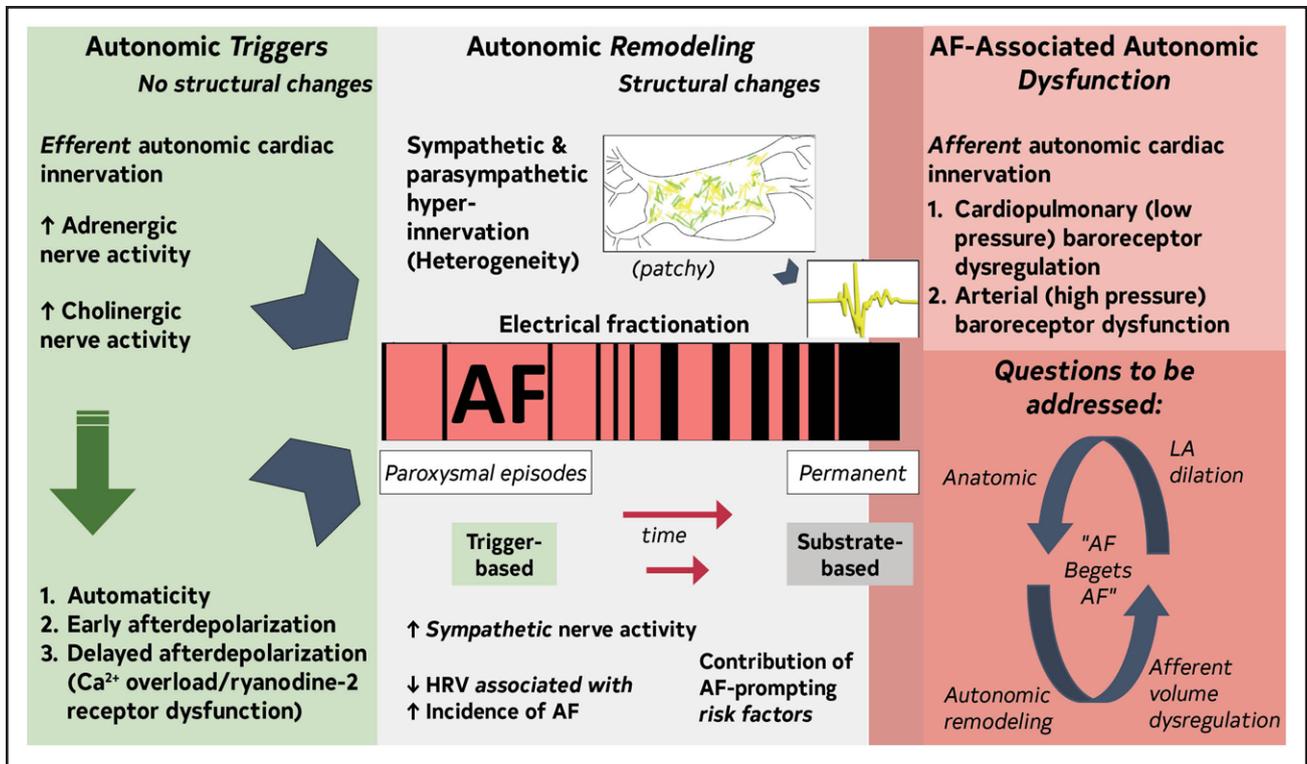
**ANS maintains AF**

Atrial sympathetic and parasympathetic hyperinnervation and spatial heterogeneity, coupled with electrical fractionation and altered atrial electrophysiology, contribute to substrate.<sup>7-10</sup> Modifiable AF risk factors promote ANS dysfunction.<sup>3</sup> AF produces autonomic afferent reflex deficiencies elicited by decreased cardiac volume<sup>11,12</sup> and increases sympathetic activity.<sup>13</sup> Afferent abnormalities disrupt blood volume and pressure homeostasis. Similar abnormalities to AF were identified in HF.<sup>14</sup> Afferent ANS dysfunction could link autonomic with anatomic remodeling (atrial dilatation<sup>15</sup>), contributing to AF self-perpetuation.

**2.4. Genetics**

Both common forms and familial AF are heritable.<sup>1-3</sup> Multiple recent genome-wide association studies have documented >100 loci specific for AF.<sup>4,5</sup> Numerous AF loci appear consistent across multiethnic groups,<sup>5</sup>

with some population variation.<sup>6,7</sup> With large genome-wide genotyped cohorts such as the UK Biobank and the US National Heart, Lung, and Blood Institute's (NHLBI's) Trans Omics for Precision Medicine, the genetic architecture of AF is now emerging. A UK Biobank study identified *TTN* loss of function variants in 0.44% of participants, 14% of whom had AF.<sup>8</sup> In a Trans Omics for Precision Medicine study of nearly 1300 participants <66 years of age with AF, 10.1% harbored a disease-associated genetic variant in genes associated with inherited cardiomyopathy or arrhythmia syndromes (most common were *TTN*, *MYH7*, *MYH6*, *LMNA*, and *KCNQ1*), and 62.8% had variants of undetermined significance. Disease-associated variants were more prevalent at younger age of AF onset, 16.8% in those <30 years.<sup>9</sup> A smaller study of persons of Hispanic or African American descent reported 7% of persons with AF onset at ≤66 years of age harbored rare likely pathogenic or pathogenic sequence variants, mostly in myocardial structural proteins and ion channels.<sup>10</sup>



**Figure 8. Contemporary Summary of the Role of the ANS in AF.**

Original figure created by the 2023 Atrial Fibrillation Guideline Writing Committee. AF indicates atrial fibrillation; ANS, autonomic nervous system; HRV, heart rate variability; and LA, left atrium.

### 2.5. Addressing Health Inequities and Barriers to AF Management

Recommendation to Address Health Inequities and Barriers to AF Management		
Referenced studies that support the recommendation are summarized in the Online Data Supplement.		
COR	LOE	Recommendation
1	B-NR	1. Patients with AF, regardless of sex <sup>1</sup> and gender diversity, race and ethnicity, <sup>2</sup> or adverse social determinants of health (SDOH), <sup>3,4</sup> should be equitably offered guideline-directed stroke risk reduction therapies as well as rate or rhythm control strategies and LRFM as indicated to improve quality of life (QOL) and prevent adverse outcomes.

<sup>1</sup>Including lower income, lower education, inadequate or lack of insurance coverage, or rurality.<sup>3-5</sup>

#### Synopsis

Inequities in AF care and outcomes in individuals who are women, from underrepresented racial and ethnic groups (UREGs),<sup>2</sup> or who have adverse SDOH have been documented.<sup>3,4</sup> Sex differences in AF treatment have been described with respect to anticoagulation<sup>6,7</sup> and rhythm control therapy approaches.<sup>7-9</sup> Racial and ethnic differences in clinical presentation, management, and prognosis, including stroke, HF, and death, in patients with AF are widely reported.<sup>2,10</sup>

To avoid guidelines having the unintended consequence of widening inequities in clinical care and

outcomes in individuals with AF, it is essential to longitudinally measure the receipt of AF GDMT and outcomes at the clinical practice and health system levels stratified by specific populations who have historically experienced inequitable care. If inequities are identified, barriers to GDMT should be eliminated. Data are needed to assess the impact of addressing SDOH in patients with AF on process measures, health care utilization, costs, and clinical outcomes.<sup>11</sup> In other health contexts, there are observational and randomized data<sup>12</sup> that screening and addressing SDOH leads to improved medication adherence,<sup>13</sup> risk factor control,<sup>14</sup> and clinical outcomes.<sup>15</sup>

#### Recommendation-Specific Supportive Text

1. Despite the elevated risk of stroke in women and several UREGs, many are less likely to be treated with stroke risk reduction therapies.<sup>6,7</sup> Although women and individuals from UREGs with AF are more symptomatic and report worse QOL than their counterparts, they also are less likely to be referred to an electrophysiologist<sup>7</sup> and receive catheter ablation.<sup>2,7-9,16</sup> Women are referred for ablation later in the disease course and at older ages than men.<sup>7,17,18</sup> These differences or delays in therapy may result in worse outcome given early rhythm control of AF improves outcomes<sup>1,19</sup> in select patients. In addition, in the Catheter

Ablation versus Antiarrhythmic Drugs in AF trial, individuals from UREGs treated with catheter ablation had a 72% relative reduction in the all-cause mortality rate.<sup>20</sup> Therefore, ensuring timely and equitable referral of women, individuals from UREG, and those with adverse SDOH for rhythm control therapy is important. In patients with AF, indicators of lower socioeconomic status were associated with lower oral anticoagulation rates,<sup>21</sup> lower rate of adherence during direct oral anticoagulant (DOAC) initiation,<sup>22</sup> specialty care,<sup>21,23</sup> and less use of cardioversion<sup>4,21</sup> and catheter ablation.<sup>4,21,24</sup> Indicators of socioeconomic disadvantages, such as increased risk of hospitalization,<sup>25</sup> stroke,<sup>4,21</sup> HF,<sup>4,21,26</sup> and death, were also associated with complications in patients with AF.<sup>4,21,27</sup>

### 3. SHARED DECISION-MAKING (SDM) IN AF MANAGEMENT

Recommendation for SDM in AF Management		
Referenced studies that support the recommendation are summarized in the Online Data Supplement.		
COR	LOE	Recommendation
2b	B-R	1. In patients with AF, the use of evidence-based decision aids might be useful to guide stroke reduction therapy treatment decisions throughout the disease course to improve engagement, decisional quality, and patient satisfaction. <sup>1-4</sup>

#### Synopsis

There are wide variations in how SDM is implemented in clinical care settings.<sup>5,6</sup> Decision aids may provide standardization of SDM approaches for better informing patients about stroke reduction therapies and improve patient-reported measures but to date have not consistently been developed with recommended frameworks, have rarely been tested in systemically disadvantaged populations (low health literacy, UREGs, low socioeconomic status, rural geography, older adults), and have had variable impact on adherence and clinical outcomes.<sup>1-8</sup> Ongoing work will measure health and digital literacy and strengthen the evidence for the impact of decision aids on decisional quality, adherence to treatment, and health outcomes.<sup>9</sup>

Symptom severity strongly correlates with QOL; thus, minimizing symptoms is an essential component of patient-centered AF management decisions. Rhythm control strategies improve QOL, particularly when maintenance of sinus rhythm or low AF burden is achieved.<sup>10</sup> Notably, few SDM decision aids are focused on rate or rhythm control treatment options, and few have measured QOL as an outcome.<sup>3,5</sup>

#### Recommendation-Specific Supportive Text

1. Recently, 2 comprehensive reviews of decision aids for stroke reduction therapies were

conducted to determine the impact of these tools on patient-reported measures of decisional quality, while considering other important outcomes including oral anticoagulant (OAC) uptake, medication adherence, and the effect on bleeding and stroke.<sup>3,4</sup> Most decision aids focused on patient-reported measures, and few underwent rigorous pilot testing or correlated the aid with clinical outcomes, such as stroke and bleeding. Decision aids consistently demonstrate improvements in patient knowledge. The pooled analysis by Song et al noted lower decisional conflict using decision aids and enhanced OAC uptake (risk ratio, 1.03 [95% CI, 1.01-1.05]).<sup>4</sup> Decision aids have historically shown marginal improvement in 3-month measures of adherence, and the 2 largest randomized trials to date showed no improvement in adherence between decision aids and usual care at 1 year.<sup>1,2</sup> There is a paucity of data on the impact of decision aids on stroke, thromboembolic events, or bleeding, and when assessed the benefit has been minimal or neutral.<sup>4,11</sup> Despite the US Centers for Medicaid & Medicare Services coverage decision requirement for SDM for percutaneous left atrial appendage occlusion (LAAO), only 1 tool was identified that incorporated this option (Table 5).<sup>5</sup>

### 4. CLINICAL EVALUATION

#### 4.1. Risk Stratification and Population Screening

There are >20 risk prediction models for incident AF in the community.<sup>1</sup> The most widely replicated risk prediction model for newly diagnosed AF is CHARGE-AF (Cohorts for Heart and Aging Research in Genomic Epidemiology model for atrial fibrillation; Table 6),<sup>2</sup> while the C<sub>2</sub>HES<sub>2</sub> score (coronary artery disease or chronic obstructive pulmonary disease [1 point each]; hypertension [1 point]; elderly [age ≥75 years, 2 points]; systolic HF [2 points];

**Table 5. Publicly Available Decision Aids**

Agency	Website	Focus Area
American College of Cardiology Colorado Program for Patient Centered Decisions	<a href="https://patientdecisionaid.org/icd/atrial-fibrillation/">https://patientdecisionaid.org/icd/atrial-fibrillation/</a>	Stroke risk reduction therapies
Anticoagulation Choice Decision Aid	<a href="https://anticoagulationdecisionaid.mayoclinic.org/">https://anticoagulationdecisionaid.mayoclinic.org/</a>	Stroke risk reduction therapies
Ottawa Hospital Research Institute Developer Healthwise	<a href="https://decisionaid.ohri.ca/AZlist.html">https://decisionaid.ohri.ca/AZlist.html</a>	AF ablation Stroke risk reduction
Stanford	<a href="https://afibguide.com/">https://afibguide.com/</a>	Stroke risk reduction therapies

**Table 6. CHARGE-AF Risk Score for Detecting Incident AF\***

Variable (X)	Estimated $\beta$ Coefficient (SE)	HR (95% CI)
Age (per 5-y increment)	0.508 (0.022)	1.66 (1.59-1.74)
White race	0.465 (0.093)	1.59 (1.33-1.91)
Height (per 10-cm increment)	0.248 (0.036)	1.28 (1.19-1.38)
Weight (per 15-kg increment)	0.115 (0.033)	1.12 (1.05-1.20)
Systolic BP (per 20-mm Hg increment)	0.197 (0.033)	1.22 (1.14-1.30)
Diastolic BP (per 10-mm Hg increment)	-0.101 (0.032)	0.90 (0.85-0.96)
Smoking (current versus former/never)	0.359 (0.063)	1.42 (1.25-1.60)
Diabetes (yes)	0.237 (0.073)	1.27 (1.64-2.48)
Myocardial infarction (yes)	0.496 (0.089)	1.64 (1.38-1.96)

Table 6 does not encompass all complications.

\*Five-year risk is given by:  $1 - 0.9718412736^{\exp(2\beta X - 12.4411305)}$ , where  $\beta$  is the regression coefficient (column 2) and X is the level of each variable risk factor.<sup>2</sup>

AF indicates atrial fibrillation; BP, blood pressure; CHARGE-AF, Cohorts for Heart and Aging Research in Genomic Epidemiology model for atrial fibrillation; HR, hazard ratio; and SE, standard error.

thyroid disease [hyperthyroidism, 1 point]) was derived and validated in Asian cohorts (Table 7).<sup>3,4</sup>

Screening for AF has been investigated, mostly in patients >65 years of age, using various protocols that include both 1-time electrocardiographic recordings, recurring intermittent ECGs (including consumer-based devices), or continuous electrocardiographic external monitors. Most screening trials have shown higher AF detection using intermittent or continuous electrocardiographic recordings<sup>5</sup> and higher AF detection in patients with higher predicted risk for AF.<sup>6</sup> A recent study also showed that an AI algorithm able to risk-stratify a relatively uniform population (eg, older adults at risk for stroke) to detect undiagnosed AF during short-term cardiac monitoring was associated with increased AF.<sup>7</sup> Conversely, mass population screening with a smartwatch app only rarely detected a new diagnosis of AF.<sup>8</sup> Ultimately, for risk stratification models and screening programs to be useful, they would need to improve outcomes and be

**Table 7. C<sub>2</sub>HEST Risk Score for Detecting Incident AF\***

Acronym	Risk Factor	Points
<b>C<sub>2</sub></b>	CAD/COPD	1-2
<b>H</b>	Hypertension	1
<b>E</b>	Elderly (age $\geq 75$ y)	2
<b>S</b>	Systolic heart failure	2
<b>T</b>	Thyroid disease (hyperthyroidism)	1

\*Total points 0-8. For the C<sub>2</sub>HEST score, the C statistic was 0.749, with 95% CI of 0.729-0.769.<sup>10</sup> The incident rate of AF increased significantly with higher C<sub>2</sub>HEST scores.

AF indicates atrial fibrillation; CAD, coronary artery disease; C<sub>2</sub>HEST, coronary artery disease or chronic obstructive pulmonary disease [1 point each]; hypertension [1 point]; elderly [age  $\geq 75$  y, 2 points]; systolic HF [2 points]; thyroid disease [hyperthyroidism, 1 point]; and COPD, chronic obstructive pulmonary disease.

cost-effective.<sup>9</sup> It is not yet established that patients at high risk of developing AF by a validated risk score benefit from screening and interventions to improve rates of ischemic stroke, systemic embolism, and survival.

## 4.2. Basic Evaluation

### 4.2.1. Basic Clinical Evaluation

Recommendations for Basic Clinical Evaluation		
Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	B-NR	1. In patients with newly diagnosed AF, a transthoracic echocardiogram <sup>1-4</sup> to assess cardiac structure, laboratory testing to include a complete blood count, metabolic panel, and thyroid function, <sup>5-7</sup> and when clinical suspicion exists, targeted testing to assess for other medical conditions associated with AF are recommended to determine stroke and bleeding risk factors, as well as underlying conditions that will guide further management.
3: No benefit	B-NR	2. In patients with newly diagnosed AF, protocolized testing for ischemia, acute coronary syndrome (ACS), and pulmonary embolism (PE) should not routinely be performed to assess the etiology of AF unless there are additional signs or symptoms to indicate those disorders. <sup>8-10</sup>

### Synopsis

The initial clinical evaluation of the patient with newly diagnosed or suspected AF should be focused on confirming the diagnosis and identifying relevant clinical factors that will impact management. A targeted history and physical examination should be performed at the initial assessment and repeated during periodic follow-up, especially given the evolving risk of thromboembolism and the cadence of symptoms in response to therapy (see Section 11, "Future Research Needs"). An ECG can assess other electrical abnormalities, including possible substrates such as Wolff-Parkinson-White (WPW) syndrome, coexisting atrial arrhythmias, as well as abnormalities that may affect decision-making in pharmacological management (eg, bradycardia, QT duration). Basic laboratory tests should be performed to determine if other clinically relevant disorders are present and impact on management, particularly with respect to stroke and bleeding risk. A transthoracic echocardiogram provides information on chamber size, thickness, function, and the presence of valvular pathology. Additional testing, including multimodality advanced imaging and further ambulatory electrocardiographic monitoring, may be pursued based on the results of these initial evaluations. AF itself does not increase the likelihood of myocardial ischemia, ACS or PE, and therefore routine testing for these disorders in the absence of signs or symptoms is of no benefit.

### Recommendation-Specific Supportive Text

1. A transthoracic echocardiogram is essential to evaluate chamber size and function, valve function,

and right ventricular (RV) pressure. Left ventricular ejection fraction (LVEF) impacts decisions for antiarrhythmic drug therapy and whether to prioritize other rhythm control therapies, including catheter ablation. Additionally, strain imaging may suggest an underlying infiltrative cardiomyopathy, such as amyloidosis.<sup>1</sup> Echocardiography also provides information on LA size and function. Altered LA compliance is known to be associated with AF<sup>11</sup> and progression toward persistent-type AF.<sup>2</sup> In a meta-analysis, AF recurrence after ablation was associated with a lower LA strain,<sup>3</sup> while LA volume was a stronger predictor of recurrence after ablation than the characterization of AF as paroxysmal or persistent.<sup>4</sup> Laboratory testing can detect other medical conditions that are associated with AF and would impact therapeutic decision-making, such as CKD,<sup>5</sup> liver dysfunction,<sup>6</sup> and hyperthyroidism.<sup>7,12</sup> Laboratory testing may also reveal electrolyte abnormalities, including from medications such as diuretics. Laboratory testing is also needed to determine stroke risk and bleeding risk factors, which will guide management decisions. When clinical suspicion exists, additional testing might be needed to evaluate for potentially related conditions, such as significant valvular disease.

2. The presence of AF itself should not prompt routine protocolized testing for myocardial ischemia, ACS, or PE, in the absence of signs or symptoms to suggest those diseases. A retrospective analysis of asymptomatic patients with AF compared with age- and sex-matched controls that were referred for myocardial stress imaging found no difference in mean summed stress score or rate of abnormal studies.<sup>8</sup> A retrospective analysis of 1700 asymptomatic AF patients (no chest pain or dyspnea) found that 4.6% had >5% ischemic myocardium, and the yield to detect ischemia that resulted in revascularization was only 0.4%.<sup>9</sup> Among patients suspected of PE, a retrospective analysis showed that the presence of AF did not increase the probability of PE.<sup>10</sup> Certainly, this would not preclude from evaluating patients with signs and/or symptoms of ischemia and PE.

**4.2.2. Rhythm Monitoring Tools and Methods**

Recommendations for Rhythm Monitoring Tools and Methods Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	B-NR	1. Among individuals without a known history of AF, it is recommended that an initial AF diagnosis be made by a clinician using visual interpretation of the electrocardiographic signals, regardless of the type of rhythm or monitoring device. <sup>1-5</sup>

Recommendations for Rhythm Monitoring Tools and Methods (Continued)		
COR	LOE	Recommendations
1	B-NR	2. In patients with an intracardiac rhythm device capable of a diagnosis of AF, such as from an atrial pacemaker lead, a diagnosis of AF should only be made after it is visually confirmed by reviewing intracardiac tracings to exclude signal artifacts and other arrhythmias. <sup>6-9</sup>
2a	B-R	3. For patients who have had a systemic thromboembolic event without a known history of AF and in whom maximum sensitivity to detect AF is sought, an implantable cardiac monitor is reasonable. <sup>10,11</sup>
2a	B-NR	4. Among patients with a diagnosis of AF, it is reasonable to infer AF frequency, duration, and burden using automated algorithms available from electrocardiographic monitors, implantable cardiac monitors, and cardiac rhythm devices with an atrial lead, recognizing that periodic review can be required to exclude other arrhythmias. <sup>1,4,5,12</sup>
2a	B-R	5. Among patients with AF in whom cardiac monitoring is advised, it is reasonable to recommend use of a consumer-accessible electrocardiographic device that provides a high-quality tracing to detect recurrences. <sup>13</sup>

**Synopsis**

Monitoring options for AF include a standard 12-lead ECG, continuously recording or loop-recording electrocardiographic monitors using separate electrodes or as patches, implantable cardiac monitors (sometimes referred to as implantable loop recorders), cardiac rhythm management devices with an atrial lead (eg, pacemakers and defibrillators), handheld ECGs, and smartwatches. Photoplethysmography has been used to infer AF from irregular pulse patterns using a variety of devices, predominately smartphone cameras<sup>14</sup> and smartwatches.<sup>15-18</sup> Electrocardiographic monitors often deploy automated algorithms for AF detection, but due to variable accuracy,<sup>1-5</sup> the initial diagnosis should rely on a health care professional's examination of the electrocardiographic tracing. Although photoplethysmography monitors may alert individuals to obtain an electrocardiographic tracing, it is not sufficiently reliable to establish an AF diagnosis.<sup>14-18</sup> AF detected from an atrial lead has been validated versus surface ECGs<sup>6,7</sup> and independently predicts stroke.<sup>8,9</sup> RCTs have demonstrated that implantable cardiac monitors exhibit the highest sensitivity in detecting AF compared with external ambulatory monitors, likely related to the longer duration of monitoring.<sup>10,11</sup> Automated algorithms to analyze electrocardiographic devices have generally been found to be sufficiently reliable to infer the frequency, duration, and burden of AF among those with an AF diagnosis.<sup>1,4,5,12</sup> A randomized trial showed that a handheld electrocardiographic monitor resulted in earlier detection of recurrent AF.<sup>13</sup>

### Recommendation-Specific Supportive Text

1. Although automated algorithms in various devices are generally reliable, health care professional overread of electrocardiographic tracings remains necessary given the imperfect test characteristics of those algorithms.<sup>1–5</sup> Similarly, while algorithms utilizing photoplethysmography signals (derived using smartphones or smartwatches) to infer irregular heart rates can discriminate AF from normal sinus rhythm, these are not sufficiently reliable to establish an AF diagnosis.<sup>14–18</sup>
2. Cardiac rhythm devices with an atrial lead have been shown to detect AF validated against conventional surface electrocardiographic tracings.<sup>6–8</sup> In addition, both the presence and duration of AF detected solely by these devices predict stroke in a manner that would be expected of AF.<sup>8,9</sup> It is still essential that the intracardiac tracings are reviewed for confirmation because false-positives are possible. The duration of AF that mandates intervention with anticoagulation will be discussed in **Section 6.4.1 (“Oral Anticoagulation for Device-Detected Atrial High-Rate Episodes Among Patients Without a Previous Diagnosis of AF”)**.
3. The more frequent and longer monitoring for AF is deployed, the greater the sensitivity in detecting AF.<sup>10,19</sup> Randomized trials, predominately among cryptogenic stroke patients, have revealed that implantable cardiac monitors exhibit the highest sensitivity in detecting AF in view of extended monitoring periods compared with external monitors.<sup>10,11</sup>
4. It is often not feasible to manually review all electrocardiographic strips from various monitoring devices, either due to inaccessibility or time and resource constraints on health care professionals. Although variability in accuracy across different devices may be present, the validity demonstrated in automated algorithms is generally sufficient to infer frequency, duration, and burden of AF using electrocardiographic devices such as continuously wearable monitors, implantable cardiac monitors, and cardiac rhythm devices with an atrial lead.<sup>1,4,5,12</sup>
5. Cardiac monitoring may be advised to AF patients for various reasons, such as for detecting recurrences, screening, or response to therapy. Among patients with AF who are undergoing cardioversion or AF ablation, a single-center, randomized trial demonstrated that use of a self-administered handheld ECG resulted in earlier detection of recurrent AF<sup>13</sup> and possibly improvement in survey-determined AF-related QOL<sup>20</sup> compared with usual care.

## 5. LIFESTYLE AND RISK FACTOR MODIFICATION (LRFM) FOR AF MANAGEMENT

### 5.1. Primary Prevention

**Recommendation for Primary Prevention**  
Referenced studies that support the recommendation are summarized in the [Online Data Supplement](#).

COR	LOE	Recommendation
1	B-NR	1. Patients at increased risk of AF should receive comprehensive guideline-directed LRFM for AF, targeting obesity, <sup>1</sup> physical inactivity, <sup>2</sup> unhealthy alcohol consumption, <sup>3</sup> smoking, <sup>4</sup> diabetes, <sup>5</sup> and hypertension. <sup>6</sup>

### Synopsis

The clinical, family history, and genetic risk factors for AF are well established (Table 3), and risk prediction models (**Section 4.1, “Risk Stratification and Population Screening”**) for AF have been reported and replicated.<sup>7–9</sup> Multiple reports have established that maintenance of optimal risk factors and ideal cardiovascular health are associated with substantially reduced risk of AF<sup>10,11</sup> onset and complications (**Section 5, “Lifestyle and Risk Factor Modification [LRFM] for AF Management”**). To reduce risk of AF onset, individuals in the general population, particularly those at increased risk of AF, should receive comprehensive integrated LRFM, including maintenance of ideal weight and weight loss if overweight or obese<sup>1,12</sup>; pursue a physically active lifestyle,<sup>2</sup> particularly if sedentary; receive smoking cessation counseling and/or medications<sup>4</sup>; moderate ( $\leq 1$  standard alcoholic drink/day) or abstain from alcohol and avoidance of binge drinking<sup>3</sup>; control diabetes<sup>5</sup>; and control BP in accordance with GDMT.<sup>6,13</sup> There is also an association of cannabis, cocaine, methamphetamine, or opiate use with increased incidence of AF.<sup>14</sup>

### Recommendation-Specific Supportive Text

1. Most cardiovascular risk factors are associated with increased risk of new-onset AF. Observational studies have demonstrated that obesity and physical inactivity each independently increase the risk of newly diagnosed AF.<sup>1,2,12,15–20</sup> However, caution should be considered in pursuing years of regular, high-volume ( $\geq 3$  h/day) high-intensity endurance training given observational data linking it with increased AF risk<sup>21–23</sup> in men and similar “J” curve risk curve observed for high or vigorous activity in both men and women in another study.<sup>24</sup> Alcohol consumption enhances the risk of AF in a fairly linear fashion, with clear evidence that binge drinking heightens the risk.<sup>3,25–29</sup> Uncertainty persists regarding harms or benefits of no more than 1 regular drink per day.<sup>28,29</sup> Self-reported,<sup>4</sup> biomarker-verified,<sup>30</sup> and genetically predicted<sup>31</sup> smoking is

associated with increased risk, and smoking cessation is associated with decreased risk of incident AF.<sup>4</sup> The presence of either type 1 or type 2 diabetes increases AF risk,<sup>5,32</sup> with evidence that worse glucose control correlates with a higher probability of developing AF.<sup>33</sup> Hypertension is the risk factor with the highest attributable risk for AF<sup>10</sup>; intensive BP control lowers the risk of incident AF in observational and randomized data.<sup>6</sup> Effective strategies to manage risk factors and prevent CVD have been reported elsewhere.<sup>12,13</sup>

## 5.2. Secondary Prevention: Management of Comorbidities and Risk Factors

### 5.2.1. Weight Loss in Individuals Who Are Overweight or Obese

Recommendation for Weight Loss in Individuals Who Are Overweight or Obese Referenced studies that support the recommendation are summarized in the Online Data Supplement.		
COR	LOE	Recommendation
1	B-R	1. In patients with AF who are overweight or obese (with body mass index [BMI] >27 kg/m <sup>2</sup> ), weight loss is recommended, with an ideal target of at least 10% weight loss to reduce AF symptoms, burden, recurrence, and progression to persistent AF. <sup>1-4</sup>

#### Synopsis

Obesity is associated with the development and progression of AF.<sup>5</sup> It results in direct changes to the atrial myocardium forming the substrate for AF.<sup>6-8</sup> In addition, obesity is also associated with several comorbidities that have been independently associated with the development of AF.<sup>9,10</sup> Obesity has a significant adverse impact on attempts to maintain sinus rhythm, with each 5-unit increase in BMI being associated with a 10% and 13% greater risk of postoperative and postablation AF, respectively.<sup>5,11,12</sup> Management of weight is important in the prevention and treatment of AF.

#### Recommendation-Specific Supportive Text

1. In an RCT in overweight and obese individuals with BMI >27 kg/m<sup>2</sup> and AF, weight loss, as part of a comprehensive LRFM program, was associated with reduction in arrhythmia symptoms, recurrence, and burden.<sup>1</sup> Observational studies demonstrated graded responses commensurate with the degree of weight loss, with achievement of at least 10% weight loss associated with greater maintenance of sinus rhythm,<sup>2</sup> improved ablation outcomes,<sup>3</sup> and reversal of AF type.<sup>4</sup> In observational studies, bariatric surgery in Class III obese individuals (BMI ≥40 kg/m<sup>2</sup>) with AF was associated with improved sinus rhythm maintenance after catheter ablation<sup>13,14</sup> and reversal of AF type.<sup>15</sup> The greater number of risk factors managed associated with likelihood of maintaining sinus rhythm.<sup>16</sup> However,

a small observational study in individuals with obesity (BMI ≥30 kg/m<sup>2</sup>) with long-lasting persistent AF observed no difference in symptoms or sinus rhythm maintenance despite significant weight loss, suggesting that there may be extreme substrates in which a weight loss strategy may not be effective.<sup>17</sup>

Structured programs with regular review of progress facilitate achievement of weight loss and appear essential, as demonstrated by inability to reduce AF burden in a small RCT that achieved only 4.5% weight loss in the intervention arm.

### 5.2.2. Physical Fitness

Recommendation for Physical Fitness Referenced studies that support the recommendation are summarized in the Online Data Supplement.		
COR	LOE	Recommendation
1	B-R	1. In individuals with AF, moderate-to-vigorous exercise training to a target of 210 minutes per week is recommended to reduce AF symptoms <sup>1-3</sup> and burden, <sup>2,3</sup> increase maintenance of sinus rhythm, <sup>3-5</sup> increase functional capacity, and improve QOL. <sup>3,5,6</sup>

<sup>1</sup>In patients without AF related to excessive exercise training.

#### Synopsis

Randomized trials provide evidence that prescribed aerobic exercise interventions may reduce arrhythmia burden in those with nonpermanent AF<sup>2</sup> and improve functional capacity and health-related QOL in both permanent<sup>1,6</sup> and nonpermanent AF.<sup>2</sup> In the ACTIVE-AF (An Exercise and Physical Activity Program in Patients With Atrial Fibrillation) study, an exercise intervention combining home and supervised aerobic exercise over 6 months resulted in greater freedom from arrhythmia recurrence, reduced burden, and improved QOL.<sup>3</sup>

#### Recommendation-Specific Supportive Text

1. In patients with nonpermanent AF, aerobic exercise training may contribute to a reduction in AF burden and improve maintenance of sinus rhythm.<sup>2-5</sup> Aerobic exercise interventions reduce severity of AF symptoms, increase functional capacity, and improve health-related QOL among patients with both nonpermanent and permanent AF.<sup>1,3,6</sup> Initiation of or continuing regular exercise after development of AF was associated with a lower risk of HF and mortality in a population-based cohort study.<sup>7</sup> Exercise training should be moderate- to vigorous-intensity aerobic exercise, with a target of 210 minutes per week, and should be prescribed to reduce the frequency and duration of AF episodes, while improving cardiorespiratory fitness and symptom severity.<sup>3</sup> Exercise prescription may be further modified to patient comorbidities, such as obesity, hypertension, and diabetes.<sup>4</sup> Caution should be applied to ensure adequate ventricular rate control during exercise training and absence of atrial

myopathy related to excessive exercise training. To date, there is little evidence that high-intensity aerobic exercise may be favorable over moderate-intensity activities,<sup>8</sup> and extreme levels of exercise have been associated with higher incidence of AF.<sup>9,10</sup> Exercise training may be delivered as a stand-alone intervention or as a component of multidisciplinary cardiac rehabilitation. Exercise-based cardiac rehabilitation improves QOL and functional capacity among patients with AF undergoing ablation,<sup>11,12</sup> although available studies have not been adequately powered to assess AF-specific outcomes, such as arrhythmia recurrence.<sup>13</sup> There is mixed evidence for a reduction in hospitalization or all-cause mortality with exercise training or exercise-based cardiac rehabilitation.<sup>12,14,15</sup>

### 5.2.3. Smoking Cessation

Recommendation for Smoking Cessation Referenced studies that support the recommendation are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendation
1	B-NR	1. Patients with a history of AF who smoke cigarettes should be strongly advised to quit smoking and should receive GDMT for tobacco cessation <sup>12</sup> to mitigate increased risks of AF-related cardiovascular complications and other adverse outcomes. <sup>3-6</sup>

#### Synopsis

Observational data support that cigarette smoking in individuals with AF is associated with worse cardiovascular outcomes and death and that individuals with AF who quit smoking are less likely to develop stroke or die. Despite the benefits of smoking cessation, individuals with AF are less likely to receive smoking cessation management than counterparts without AF.<sup>78</sup> Patients with AF should be strongly advised to quit cigarette smoking<sup>9</sup> and should receive GDMT for tobacco cessation, including behavioral interventions<sup>10,11</sup> and pharmacotherapy.<sup>2</sup>

#### Recommendation-Specific Supportive Text

1. In individuals with AF, cigarette smoking was associated with poorer outcomes. For individuals who have undergone AF catheter ablation, current cigarette smoking was associated with increased risk for AF recurrence.<sup>12,13</sup> Cigarette smoking was associated with less time in therapeutic range for patients on warfarin.<sup>14</sup> Although some heterogeneity exists, the preponderance of studies have reported that individuals with AF who smoked cigarettes had increased risks of stroke,<sup>3,4</sup> HF,<sup>5</sup> hospitalization,<sup>6</sup> and death.<sup>6,15</sup> Of concern, studies have reported that individuals with AF (versus those without) were less likely to receive smoking cessation interventions.<sup>78</sup> Observational studies suggest that compared with current smokers, individuals with AF who quit smoking after AF diagnosis were

less likely to experience CVD,<sup>3</sup> stroke,<sup>3,16</sup> and all-cause mortality.<sup>16</sup>

### 5.2.4. Alcohol Consumption

Recommendation for Alcohol Consumption Referenced studies that support the recommendation are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendation
1	B-R	1. Patients with AF seeking a rhythm-control strategy should minimize or eliminate alcohol consumption to reduce AF recurrence and burden. <sup>1-3</sup>

#### Synopsis

Among patients with a diagnosis of AF, randomized trials have demonstrated a reduction in AF burden on assignment to abstinence,<sup>1</sup> that alcohol acutely changes human electrophysiology in a fashion that renders the atria more prone to fibrillate,<sup>2</sup> and suggest that avoiding alcohol can reduce the risk of a near-term AF event.<sup>3</sup>

#### Recommendation-Specific Supportive Text

1. Among patients with AF, a case-crossover study revealed a higher risk of a discrete AF episode hours after objectively confirmed alcohol consumption.<sup>4</sup> In the context of a structured comprehensive management of risk factors, alcohol abstinence<sup>1</sup> or reduction to  $\leq 3$  standard drinks per week has been demonstrated to reduce AF symptoms,<sup>5</sup> AF burden,<sup>6,7</sup> and progression of AF from paroxysmal to persistent.<sup>8</sup>

### 5.2.5. Caffeine Consumption

Recommendation for Caffeine Consumption Referenced studies that support the recommendation are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendation
3: No Benefit	B-NR	1. For patients with AF, recommending caffeine abstinence to prevent AF episodes is of no benefit, although it may reduce symptoms in patients who report caffeine triggers or worsens AF symptoms. <sup>1-9</sup>

#### Synopsis

A randomized N-of-1 trial,<sup>2</sup> as well as longitudinal, observational studies, have generally found that caffeine consumed within normal limits is either associated with no heightened risk<sup>3-6</sup> or a reduced risk of incident AF.<sup>3,5,7-9</sup> Patients often report caffeine as a trigger of AF,<sup>10</sup> although this has not been supported by objective data.

#### Recommendation-Specific Supportive Text

1. A randomized trial of caffeine failed to show any difference in postoperative AF risk,<sup>1</sup> and paroxysmal AF patients experienced no detectable difference in AF episodes when exposing themselves to versus avoiding caffeine in randomized N-of-1 trials.<sup>2</sup> Longitudinal, observational studies have generally found that caffeine consumed in usual amounts is either associated with no heightened

risk<sup>3-6</sup> or a reduced risk of incident AF.<sup>3,5,7-9</sup> Also, Mendelian randomization studies examining caffeine metabolism-related genetic variants as instrumental-variable surrogates of caffeine consumption have not shown either a harmful or protective effect related to incident AF.<sup>8,11</sup> Several case reports have described a relationship between excessive consumption of caffeine (involving overdoses or highly caffeinated energy drinks)<sup>12,13</sup> and AF in young, healthy individuals. Individuals should not begin or increase their caffeine consumption with the intent of reducing their AF risk. Patients often report that caffeine triggers their AF,<sup>10,14</sup> although this has neither been supported by nor extensively studied in an objective manner. Current studies cannot exclude the possibility of individual-level idiosyncratic relationships between caffeine and AF. It is also possible that caffeine exacerbates symptoms of AF, or causes similar symptoms of palpitations, or enhances heart rhythm awareness.

### 5.2.6. Diet and Dietary Supplementation

Promoting a healthy diet is an effective strategy for prevention of cardiovascular disease. The evidence pertaining to the prevention of AF using dietary supplements is inconsistent, complicated by substantial misclassification and difficulties controlling for potential confounding factors associated with dietary interventions.

Several studies have evaluated the role of omega-3 fatty acids and AF, demonstrating an inverse relationship between plasma omega-3 polyunsaturated fatty acid levels and prevalent AF.<sup>1,2</sup> However, with supplementation there has been no effect or a potential for greater AF.<sup>3-7</sup> Although vitamin D supplementation is not useful on a population basis,<sup>8,9</sup> its use in the perioperative period in deficient individuals reduces AF.<sup>10</sup> Similarly, ascorbic acid has been beneficial in reducing postoperative AF in some studies, although not uniformly.<sup>11</sup>

The importance of weight management on AF symptoms, burden, and recurrence is increasingly recognized,<sup>12,13</sup> leading to various dietary interventions. Although evidence on diets is still evolving, analyses of the ARIC (Atherosclerosis Risk in Communities) study caution using low-carbohydrate diets, which were found to increase the risk of incident AF, regardless of the type of protein or fat used to replace carbohydrate.<sup>14</sup>

### 5.2.7. Diabetes

AF and diabetes are associated with increased risk of cardiovascular mortality and sudden death.<sup>1</sup> In patients with diabetes, vascular mortality was lower in patients treated with DOACs compared with warfarin.<sup>2</sup> In patients with AF and diabetes undergoing catheter ablation, optimal glycaemic control preablation may lessen the risk of AF recurrence postablation.<sup>3</sup>

### 5.2.8. Treatment of Hypertension

**Recommendation for the Treatment of Hypertension**  
Referenced studies that support the recommendation are summarized in the [Online Data Supplement](#).

COR	LOE	Recommendation
1	B-NR	1. For patients with AF and hypertension, optimal BP control is recommended to reduce AF recurrence and AF-related cardiovascular events. <sup>1-7</sup>

### Synopsis

Renal denervation and mineralocorticoid receptor antagonists (MRAs) have been associated with decreased AF burden in clinical trials.<sup>1,2</sup> The only randomized trial singularly targeting BP control as a mechanism to reduce the recurrence of AF<sup>8</sup> showed no significant difference in the primary outcome of recurrent symptomatic atrial arrhythmia beyond 3 months' postablation among the 2 groups. However, clinical trials of integrated comprehensive LRFM programs in conjunction with rhythm control therapies for AF have resulted in longer arrhythmia-free survival and decreased AF burden.<sup>3,5,9</sup> Among patients with AF, treating elevated BP to guideline-directed goals reduces major cardiovascular events.<sup>9</sup>

### Recommendation-Specific Supportive Text

1. In patients with AF, treatment of hypertension should aim for current BP guidelines to reduce stroke, bleeding, and other adverse outcomes.<sup>5,10</sup> An RCT of patients with paroxysmal AF and hypertension noted fewer recurrences among participants treated with renal denervation and pulmonary vein isolation (PVI) compared with PVI alone.<sup>2</sup> Randomized studies of mineralocorticoid receptor antagonists for hypertension have been shown to reduce AF burden, and ACE inhibitors and angiotensin II receptor blockers have been associated with lower AF incidence in secondary analyses of RCTs (see [Section 8.3.4, "Upstream Therapy"](#)). In addition, several integrated LRFM programs that have resulted in a decrease in BP have been associated with a decreased recurrence of AF.<sup>3,11</sup> The SMAC (Substrate Modification With Aggressive Blood Pressure Control) AF trial randomized hypertensive patients scheduled for AF ablation to standard or aggressive BP treatment with a systolic BP target of 120 or 140 mm Hg.<sup>8</sup> No significant difference was shown in recurrent symptomatic atrial arrhythmia beyond 3 months postablation (median follow-up, 14 months), and this is the only RCT to date singularly targeting BP control as a mechanism to reduce AF recurrence.<sup>8</sup> Post hoc analyses of DOAC clinical trials to reduce the risk of stroke in patients with AF have consistently found lower rates of stroke in patients with controlled BP.<sup>6,7</sup>

### 5.2.9. Sleep

Recommendation for Sleep Referenced studies that support the recommendation are summarized in the Online Data Supplement.		
COR	LOE	Recommendation
2b	B-NR	1. Among patients with AF, it may be reasonable to screen for obstructive sleep apnea, given its high prevalence in patients with AF, although the role of treatment of sleep-disordered breathing (SDB) to maintain sinus rhythm is uncertain. <sup>1-13</sup>

#### Synopsis

SDB is a risk factor for the development of incident AF, and more severe SDB acutely increases the risk of a discrete AF episode.<sup>14-18</sup> Independent of SDB, poor sleep quality is associated with an increased risk of developing incident AF.<sup>19-21</sup> When formal testing for SDB is used, the disease is frequently observed in >20% of patients with an AF diagnosis.<sup>1-5</sup> Observational studies suggest that treatment of SDB may reduce the risk of AF recurrence and AF burden, but RCTs have not been adequately powered to reveal a relationship between treating SDB and reduced AF.<sup>6-13</sup>

#### Recommendation-Specific Supportive Text

1. The prevalence of SDB is remarkably and consistently high in patients with AF (generally substantially >20% and sometimes >50% regardless of the type of AF population assessed), is often undetected, and, as conventional symptoms of SDB may be absent, may require formal study to establish a diagnosis of SDB.<sup>1-5,11</sup> Multiple observational studies have described fewer recurrences of AF and a reduction in AF burden, including after cardioversion and catheter ablation procedures, among those undergoing treatment for SDB compared with those not treated for their SDB.<sup>6-11,22</sup> However, small trials randomizing patients with AF and SDB treatment versus usual care have not shown significant differences in AF burden or AF recurrence, including after cardioversion or PVI ablation,<sup>12,13,22</sup> although studies tended to exclude patients who might benefit most from SDB treatment (eg, those who had more symptomatic sleep apnea [Epworth Sleepiness Scale score >10 or 15], severe cardiovascular disease [LVEF <40% or 45%], or severe obesity).

### 5.2.10. Comprehensive Care

Recommendations for Comprehensive Care Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	A	1. Patients with AF should receive comprehensive care addressing guideline-directed LRFM, AF symptoms, risk of stroke, and other associated medical conditions to reduce AF burden, progression, or consequences. <sup>1-3</sup>
2a	B-R	2. In patients with AF, use of clinical care pathways, such as nurse-led AF clinics, is reasonable to promote comprehensive, team-based care and to enhance adherence to evidence-based therapies for AF and associated conditions. <sup>4-6</sup>

#### Synopsis

Almost all patients with AF have multiple conditions that either increase AF risk or are exacerbated by AF. Patients with AF are also at risk of developing thromboembolism, stroke, and HF, so a comprehensive approach tailored to the needs of the individual patient should improve outcomes. Randomized trials have shown that interventions aimed at AF risk factors, such as alcohol use, overweight, and HF, reduce AF burden. Clinical care pathways and algorithms for AF management, including LRFM, have shown promise in randomized trials through coordinating care and facilitating comprehensive AF management.

Although comprehensive care of the multiple conditions associated with AF is logical, it is unclear whether integrated care by a multidisciplinary team leads to better outcomes than comprehensive care by a single clinician applying an evidence-based AF clinical care algorithm or pathway. Nevertheless, coordination of care among multiple clinicians should also improve care, even though it has not been evaluated rigorously.<sup>7</sup>

#### Recommendation-Specific Supportive Text

1. Randomized trials have shown the efficacy of many individual components of patient-centered care for AF, as discussed earlier in this section. Several randomized and nonrandomized studies have utilized comprehensive programs for patients with AF.<sup>2,8,9</sup> The RACE 3 (Rate Control versus Electrical cardioversion for persistent atrial fibrillation) trial<sup>3</sup> found that multifaceted treatment for patients with AF and early HF (with mineralocorticoid receptor antagonists, statins, ACE inhibitors and/or angiotensin receptor blockers [ARBs], and cardiac rehabilitation) improved maintenance of sinus rhythm.
2. Various clinical care pathways, algorithms, and electronic clinical decision support systems for the care of patients with AF have been tested in clinical trials, with mixed results. Care provided by specialty nurses using a clinical support system aimed at enhancing adherence to guideline-directed therapies improved cardiovascular outcomes in a single center study<sup>4</sup> but not in the subsequent multicenter RACE 4 trial, where results were associated with experience of the center, although adherence to guideline-based recommendations was still greatly improved.<sup>10</sup> In a cluster randomized trial of elderly patients with AF where integrated care intervention consisting of (a) quarterly AF check-ups by trained nurses in primary care, also focusing on comorbidities, (b) monitoring of anticoagulation therapy in primary care, and finally (c) easy-access availability of consultations from cardiologists and anticoagulation clinics, the patients assigned to integrated care experienced a 45% reduction in all-cause mortality when compared with usual care.<sup>11</sup> In another study (SAFETY [Standard versus Atrial Fibrillation specific management study]), a posthospital discharge

management program specific to AF was associated with proportionately more days alive and out of hospital but not prolonged event-free survival relative to standard management.<sup>12</sup> On the other hand, data on technology-based clinical decision support systems are mixed, with a reduction in stroke and thromboembolism in the mAF-App 2 (Mobile Health Technology for Improved Screening and Optimized Integrated Care in Atrial Fibrillation) trial<sup>5</sup> and improved anticoagulation use in the CDS-AF (clinical decision support tool for stroke prevention) trial,<sup>6</sup> but no significant effect on primary outcomes in 3 other randomized trials.<sup>13–15</sup> Educational interventions for both providers and patients can improve use of anticoagulation.<sup>16</sup>

## 6. PREVENTION OF THROMBOEMBOLISM

### 6.1. Risk Stratification Schemes

Recommendations for Risk Stratification Schemes Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	B-NR	1. Patients with AF should be evaluated for their annual risk of thromboembolic events using a validated clinical risk score, such as CHA <sub>2</sub> DS <sub>2</sub> -VASc. <sup>1–4</sup>
1	B-NR	2. Patients with AF should be evaluated for factors that specifically indicate a higher risk of bleeding, such as previous bleeding and use of drugs that increase bleeding risk, in order to identify possible interventions to prevent bleeding on anticoagulation. <sup>5–7</sup>
2a	C-LD	3. Patients with AF at intermediate annual risk of thromboembolic events by risk scores (eg, equivalent to CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 1 in men or 2 in women), who remain uncertain about the benefit of anticoagulation, can benefit from consideration of factors that might modify their risk of stroke to help inform the decision.*
3: No Benefit	B-NR	4. In patients who are deemed at high risk for stroke, bleeding risk scores should not be used in isolation to determine eligibility for oral anticoagulation but instead to identify and modify bleeding risk factors and to inform medical decision-making. <sup>8–10</sup>

\*Factors may include AF burden or other features in Table 3.

#### Synopsis

Patients with AF have an increased risk of stroke that varies widely among individuals. Several risk scores based on clinical factors have been developed.<sup>1–3</sup> Risk scores should be evaluated using accepted criteria<sup>11</sup>: their ability to discriminate between high- and low-risk individuals (eg, as assessed by the c-index), their accurate calibration to actual risk levels, and their validation in independent populations. A patient's absolute risk of stroke is central to recommendations about anticoagulation and can be characterized as low (~<1%/y), intermediate (~1 to ~2%/y), and high (~>2%/y). Currently used risk scores discriminate moderately well between patients at higher and lower risk yet can greatly overes-

timate or underestimate absolute risk levels<sup>4</sup> in different populations. Current risk scores may be inaccurate because they omit other factors that alter risk of stroke, especially characteristics of AF<sup>12–14</sup>; consequently, risk scores should be calibrated against the actual annual rates of stroke in the target population to assure an accurate, unbiased risk prediction. Newer risk scores may modestly improve risk discrimination (c-index) compared with CHA<sub>2</sub>DS<sub>2</sub>-VASc and may offer potential advantages in specific populations (Table 8). Online calculators are available for the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation),<sup>1</sup> CHA<sub>2</sub>DS<sub>2</sub>-VASc,<sup>2</sup> and GARFIELD-AF<sup>3</sup> (Global Anticoagulant Registry in the Field-Atrial Fibrillation) risk scores.

Anticoagulation increases the risk of bleeding, so patients with AF are generally evaluated for bleeding risk as part of SDM about anticoagulation. Currently used bleeding risk scores—HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly [age ≥65 years], drugs/alcohol concomitantly),<sup>5</sup> HEMORR<sub>2</sub>HAGES (hepatic or renal disease, ethanol abuse, malignancy, older age [≥75 years], reduced platelet count or function, re-bleeding risk, hypertension [uncontrolled], anemia, genetic factors, excessive fall risk, stroke),<sup>6</sup> and ATRIA (anemia, renal disease, elderly [age ≥75 years], any prior bleeding, hypertension)<sup>7</sup>—discriminate poorly between patients with and without bleeding<sup>15</sup> and include many nonspecific factors that predict an increased risk of stroke as well as an increased risk of bleeding (eg, age, hypertension, renal disease, and previous stroke). Assessment of factors that specifically predict an increased risk of bleeding without predicting an increased risk of stroke is more helpful when balancing risks and benefits of anticoagulation.

#### Recommendation-Specific Supportive Text

1. Several risk scores based on clinical factors have been developed<sup>1–3</sup>; in general, risk discrimination is improved by including more predictors (eg, CHA<sub>2</sub>DS<sub>2</sub>-VASc improved on the original CHADS<sub>2</sub><sup>2</sup> [congestive heart failure, hypertension, age >75 years, diabetes, stroke/transient ischemia attack/thromboembolism] by adding additional risk factors and age categories). However, the absolute risk associated with any particular score level varies widely across populations; among 15 cohort studies, patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 had annual rates of stroke that ranged from low to high: <1% in 4 cohorts, 1% to 2% in 6 cohorts, and >2% in 5 cohorts,<sup>4</sup> although higher scores were associated with higher stroke risk in each cohort (Figure 9). The CHA<sub>2</sub>DS<sub>2</sub>-VASc score is considered the most validated score, most therapies have used that score to prove efficacy, and thus CHA<sub>2</sub>DS<sub>2</sub>-VASc is generally the preferred score.

**Table 8. Three Validated Risk Models for Stroke**

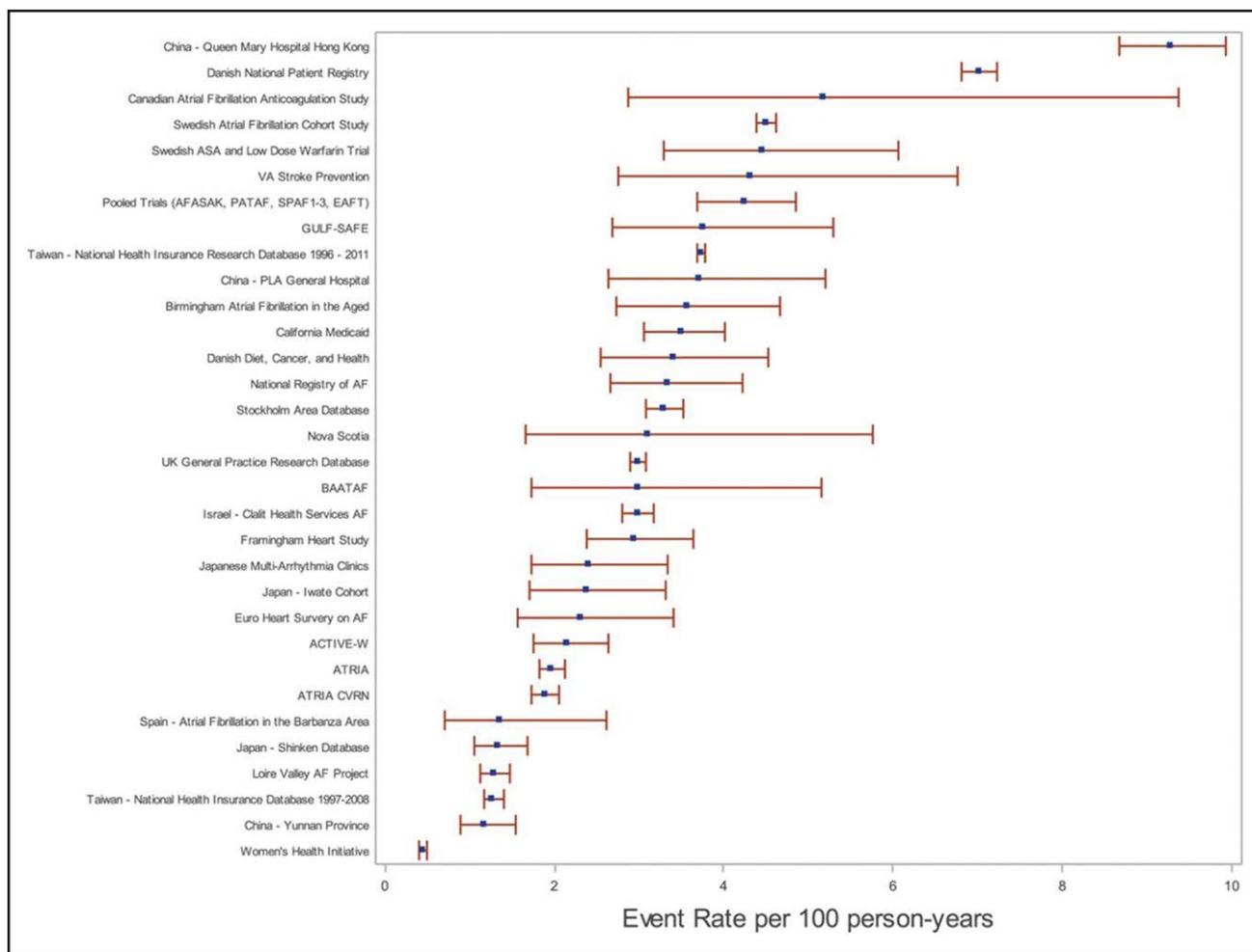
Risk Factor	CHA <sub>2</sub> DS <sub>2</sub> -VASC <sup>2</sup>	ATRIA <sup>1</sup>	GARFIELD <sup>3</sup>
Age ≥85 y		6	0.98
Age ≥75 y	2	5	0.59
Age 65-74 y	1	3	0.20
Female sex	1	1	
Hypertension	1	1	0.16
Renal disease		1	0.35
Diabetes	1	1	0.21
Current smoking			0.48
Congestive heart failure	1	1	0.23
Previous stroke or TIA	2	2–8*	0.80
Vascular disease	1		0.20
Dementia			0.51
Previous bleeding			0.30
Proteinuria		1	
Low risk score	0	0–5	0–0.89
Intermediate risk score	1	6	0.90–1.59
High risk score	≥2	7–15	≥1.60
C-index (11)	0.63	0.66	-
C-index (13)	0.67	-	0.71

\*8 points if age <65 y; 4 points if age 65–74 y; 2 points if age 75–84 y; and 3 points if ≥85 y.

ATRIA indicates Anticoagulation and Risk Factors in Atrial Fibrillation: anemia, renal disease, elderly (age ≥75 y), any previous bleeding, hypertension; CHA<sub>2</sub>DS<sub>2</sub>-VASC, indicates congestive heart failure, hypertension, age ≥75 y (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 y, sex category; GARFIELD-AF, Global Anticoagulant Registry in the Field-Atrial Fibrillation; and TIA, transient ischemic attack.

Yet, despite its extensive use, CHA<sub>2</sub>DS<sub>2</sub>-VASC has shown suboptimal performance in selected populations, such as those with renal disease, prompting the creation of other scores. Newer risk scores, such as the ATRIA<sup>1,16,17</sup> and GARFIELD-AF<sup>3,18</sup> scores, modestly improve risk discrimination (c-index) compared with CHA<sub>2</sub>DS<sub>2</sub>-VASC, but their calibration and risk reclassification performance has not been as rigorously evaluated. A recent meta-analysis reported that 19 risk scores, 329 external validations, and 76 risk score updates have been conducted to predict ischemic stroke in patients with AF.<sup>19</sup> Potential differences of the most studied risk scores are listed in Table 9. Some potential advantages of other scores, for example, the GARFIELD-AF score, includes mortality and bleeding risk to facilitate discussion with patients in a more comprehensive way. Also, when uncertainty exists, a score such as GARFIELD-AF adds additional variables to consider, such as smoking status, renal disease, and dementia. This guideline does not intend to preclude the future development of more accurate scores for stratifying patients.

- Clinical decisions surrounding stroke prevention therapy in patients with AF must balance the risks of ischemic stroke, the risks of bleeding with treatment, net clinical benefit, and patient preferences. The most studied bleeding risk scores (HAS-BLED,<sup>5</sup> HEMORR<sub>2</sub>HAGES,<sup>6</sup> and ATRIA<sup>7</sup>) discriminate poorly between patients with and without bleeding<sup>20</sup> (c-index 0.58 to 0.59 in a French nationwide study<sup>21</sup>). These scores are problematic to use in clinical decision-making because they incorporate several clinical factors that increase the risks of both stroke and bleeding (eg, age, hypertension, renal disease, and previous stroke), which makes it difficult to balance the benefits and risks of anticoagulation because the same risk factors also predict higher risk of stroke. Consideration of factors that specifically indicate a higher risk of bleeding without predicting higher risk of stroke (eg, previous bleeding, anemia, and certain medications) may better inform decision-making about the balance of benefits and harms expected from anticoagulation. Assessment of risk factors specific for bleeding may suggest interventions to reduce bleeding risk, such as discontinuing antiplatelet medications or nonsteroidal anti-inflammatory medications or the use of LAAO devices.<sup>10</sup>
- The decision to treat with OACs for stroke prevention in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASC of 1 (CHA<sub>2</sub>DS<sub>2</sub>-VASC of 2 in women) may at times require additional discussion with patients as the strength or recommendation is less robust (2a), and often patients might be more reluctant. Also, the 1-point-concept of risk estimation in the subgroup of patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASC score of 1 has shown to be simplistic because the magnitude of risk for each factor is heterogeneous and because data have shown a wide range of risk depending on the studied cohort.<sup>22</sup> Thus, as part of SDM discussions with patients, other factors, such as AF burden, can be considered when interpreting a stroke risk score.<sup>12–14,23</sup> Additional factors, such as degree of hypertension control, can also affect the risk of stroke; in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, a single elevated BP measurement during the study was associated with a 50% increased risk of stroke.<sup>23,24</sup> Additional patient-specific risk factors, such as certain biomarkers (eg, proBNP), LA or left atrial appendage (LAA) function and anatomy, or electrocardiographic features, among others, have been demonstrated to influence stroke risk, yet it is unclear how to incorporate them into clinical practice.<sup>12</sup> Antithrombotic treatment with DOACs seems to offer a superior net-benefit with regard to prevention of thromboembolic events and the risk of major bleeding compared with vitamin K antagonists (VKAs). Consideration of these



**Figure 9. Rates of Stroke by Stroke Risk Score Levels in Different Cohorts.**

Overall stroke rate in atrial fibrillation cohorts in order of descending stroke rate (events per 100 person-years). Reproduced with permission from Quinn et al.<sup>4</sup> Copyright 2017 American Heart Association, Inc.

additional factors may inform decision-making for patients with an intermediate risk of stroke who remain uncertain on deciding anticoagulation.

- Unless an absolute contraindication to anticoagulation is present, bleeding risk scores have limitation in clinical decision-making because the most commonly used scores (HAS-BLED,<sup>5</sup> HEMORR<sub>2</sub>HAGES,<sup>6</sup> and ATRIA<sup>7</sup>) are based on several clinical factors that indicate higher risks of both stroke and bleeding, and patients with higher risk of bleeding also tend to have a higher risk of stroke. Furthermore, a bleeding risk score cannot be interpreted in isolation because it does not assess the net clinical benefit of anticoagulation or balance the risk of bleeding against the risk of stroke. Population-based studies suggest that the benefits of stroke prevention with oral anticoagulation generally outweigh the risks of bleeding, even in patients determined to be at high risk for bleeding.<sup>8,9</sup> Decision-making about oral anticoagulation should be based on consideration of both benefits

and harms, not by using bleeding risk scores in isolation, and the best utility of these scores may be identifying potential modifying risk factors.<sup>8,9</sup>

## 6.2. Risk-Based Selection of Oral Anticoagulation: Balancing Risks and Benefits

Recommendations for Risk-Based Selection of Oral Anticoagulation: Balancing Risks and Benefits		
Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	B-R	1. In patients diagnosed with AF who have an estimated annual risk of stroke or thromboembolic events $\geq 2\%$ , selection of therapy to reduce the risk of stroke should be based on the risk of thromboembolism, regardless of whether the AF pattern is paroxysmal, persistent, long-standing persistent, or permanent. <sup>1-3</sup>
1	B-NR	2. In patients with AF at risk for stroke, reevaluation of the need for and choice of stroke risk reduction therapy at periodic intervals is recommended to reassess stroke and bleeding risk, net clinical benefit, and proper dosing. <sup>4,5</sup>

**Table 9. Some Best Known Published Clinical Scores With Potential Advantages**

Year of Publication, Score Name	Score Components	Potential Advantages	No. of Validation Studies <sup>19</sup>	Hyperlink to Online Score Calculator, if Available
2001 CHADS <sub>2</sub> <sup>25</sup>	CHF, hypertension, age (≥65 y is 1 point, ≥75 y is 2 points), diabetes, stroke/TIA (2 points)	CHADS <sub>2</sub> was superior to existing risk classification schemes AFI scheme: C-statistic, 0.68 (0.65–0.71) SPAF-III scheme: C-statistic, 0.74 (0.71–0.76) CHADS <sub>2</sub> score: C-statistic, 0.82 (0.80–0.84)	46	<a href="https://www.mdcalc.com/calc/40/chads2-score-atrial-fibrillation-stroke-risk">https://www.mdcalc.com/calc/40/chads2-score-atrial-fibrillation-stroke-risk</a>
2010 CHA <sub>2</sub> DS <sub>2</sub> -VASc <sub>2</sub>	CHF, hypertension, age ≥75 y, diabetes, stroke or TIA, vascular disease, age 65–74 y, female sex	Most commonly used and studied, superior to CHADS <sub>2</sub> score. C-statistic, 0.606 (0.513–0.699) for CHA <sub>2</sub> DS <sub>2</sub> -VASc score vs 0.561 (0.450–0.672) for CHADS <sub>2</sub> score Improved compared with original CHADS <sub>2</sub> score	82	<a href="https://www.mdcalc.com/calc/801/cha2ds2-vasc-score-atrial-fibrillation-stroke-risk#next-steps">https://www.mdcalc.com/calc/801/cha2ds2-vasc-score-atrial-fibrillation-stroke-risk#next-steps</a>
2013 ATRIA <sup>1</sup>	Age (65–74 y is 3 points, 75–84 y is 5 points, ≥85 y is 6 points), hypertension, diabetes, CHF, proteinuria, GFR <45 mL/min/1.73 m <sup>2</sup> , sex	Includes more age categories, renal function, and proteinuria More patients were classified as low or high risk but not as well tested in general.	11	<a href="https://www.mdcalc.com/calc/1842/atria-stroke-risk-score">https://www.mdcalc.com/calc/1842/atria-stroke-risk-score</a>
2017 GARFIELD-AF <sup>3</sup>	Web-based, uses routinely collected clinical data, and includes a total of 16 questions	Web-based tool for predicting stroke and mortality, includes the effect of the different anticoagulants, bleeding risk and mortality to facilitate shared decision-making on the potential benefits/risks of anticoagulation	4	<a href="https://af.garfieldregistry.org/garfield-af-risk-calculator">https://af.garfieldregistry.org/garfield-af-risk-calculator</a>
2016 MCHA <sub>2</sub> DS <sub>2</sub> -VASc <sup>26</sup>	Expanded lower threshold for age to 50 y (1 point for age 50–74 y)	Validated in Asian cohort Can further identify Asian AF patients who may derive benefits from stroke prevention. In 1 study, MCHA <sub>2</sub> DS <sub>2</sub> -VASc was superior to CHA <sub>2</sub> DS <sub>2</sub> -VASc C-statistics = 0.708 (0.703–0.712) vs 0.689 (0.684–0.694)	1	

ATRIA indicates Anticoagulation and Risk Factors in Atrial Fibrillation: anemia, renal disease, elderly (age ≥75 y), any previous bleeding, hypertension; CHADS<sub>2</sub>, congestive heart failure, hypertension, age >75 y, diabetes, stroke/transient ischemia attack/thromboembolism; CHA<sub>2</sub>DS<sub>2</sub>-VASc, indicates congestive heart failure, hypertension, age ≥75 y (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 y, sex category; CHF, congestive heart failure; GARFIELD-AF, Global Anticoagulant Registry in the Field-Atrial Fibrillation; GFR, glomerular filtration rate; SPAF-III, stroke prevention atrial fibrillation, and TIA, transient ischemic attack.

## Synopsis

Prevention of stroke is important in patients with AF to maximize survival, health, and QOL. Selection of stroke risk reduction therapy should be guided by the patient's risk of stroke, risks of bleeding with therapy, and their individual preferences. When considering stroke prevention therapy, the risk of stroke should inform the decision regardless of the pattern of AF (paroxysmal, persistent, long-standing persistent, or permanent). All decisions regarding stroke prevention therapy should be periodically reassessed since a patient's risk, eligibility, and preferences can change over time.

## Recommendation-Specific Supportive Text

1. Although the risk of stroke and systemic embolism and all-cause mortality are increased in persons with more persistent forms of AF, selection of stroke prevention therapy should be based on the risk of stroke and not the pattern of AF. Treatment effects with oral anticoagulation are consistent across AF patterns (paroxysmal, persistent, long-standing persistent, or permanent) in trials of stroke prevention therapy.<sup>1–3</sup>
2. AF is a lifelong condition and, thus, patient characteristics, risk factors, and net clinical benefit can and often will change over time.<sup>4</sup> In long-term follow-up, stroke risk increases due to age and

accumulation of other risk factors.<sup>6</sup> Physiologic factors that impact stroke prevention therapy also change over time and can have important implications for proper medication dosing and patient safety.<sup>5</sup> Typically, periodic assessment should be performed once a year but might need to be performed more frequently in the context of changes in clinical status, such as reduction in renal function or development of additional risk factors.

## 6.3. Oral Anticoagulants

### Vitamin K Antagonists

Since the 1950s, warfarin was used as a first-line therapy until DOACs came into practice. A narrow therapeutic window based on international normalized ratios (INRs), frequent monitoring, more frequent drug interactions (mainly through CYP2C9), dietary restrictions, and low clinical safety profile affected the routine use of warfarin in practice. Because of affordability issues of DOACs for some patients with AF, warfarin is still an appropriate OAC due to its lower cost for patients who cannot afford DOACs. About 21% of patients with nonvalvular AF were still receiving warfarin, while the rest received DOACs in the first quarter of 2017.<sup>1</sup> Warfarin remains the first-line therapy in

**Table 10. Risk Factor Definitions for CHA<sub>2</sub>DS<sub>2</sub>-VASc Score as in the Original Article<sup>2</sup>**

<b>C</b>	Heart Failure	The presence of signs and symptoms of either right (elevated central venous pressure, hepatomegaly, dependent edema) or left ventricular failure (exertional dyspnea, cough, fatigue, orthopnea, paroxysmal nocturnal dyspnea, cardiac enlargement, rales, gallop rhythm, pulmonary venous congestion) or both, confirmed by noninvasive or invasive measurements demonstrating objective evidence of cardiac dysfunction
<b>H</b>	Hypertension	A resting blood pressure >140 mm Hg systolic and/or >90 mm Hg diastolic on at least 2 occasions or current antihypertensive pharmacological treatment
<b>A<sub>2</sub></b>	Age, additional risk/point	Age ≥75 y
<b>D</b>	Diabetes	Fasting plasma glucose level ≥7.0 mmol/L (126 mg/dL) or treatment with hypoglycemic agent and/or insulin
<b>S<sub>2</sub></b>	Thromboembolism	Either an ischemic stroke, transient ischemic attack, peripheral embolism, or pulmonary embolism
<b>V</b>	Vascular Disease	Coronary artery disease (prior myocardial infarction, angina pectoris, percutaneous coronary intervention, or coronary artery bypass surgery) or peripheral vascular disease (the presence of any of the following: intermittent claudication, previous surgery or percutaneous intervention on the abdominal aorta or the lower extremity vessels, abdominal or thoracic vascular surgery, arterial and venous thrombosis)
<b>A</b>	Age standard risk/weight	Age 65–74 y
<b>Sc</b>	Sex Category	Female sex

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patients with AF and moderate-severe rheumatic mitral stenosis or mechanical heart valves. Clinical studies show that the target INR is between 2 and 3, and risk of bleeding becomes mostly apparent when INR exceeds 4. OAC use in special populations will be discussed in separate sections.

**Table 11. Additional Risk Factors That Increase Risk of Stroke Not Included in CHA<sub>2</sub>DS<sub>2</sub>-VASc**

Higher AF burden/Long duration
Persistent/permanent AF versus paroxysmal
Obesity (BMI, ≥30 kg/m <sup>2</sup> )
HCM
Poorly controlled hypertension
eGFR (<45 mL/h)
Proteinuria (>150 mg/24 h or equivalent)
Enlarged LA volume (≥73 mL) or diameter (≥4.7 cm)

AF indicates atrial fibrillation; BMI, body mass index; eGFR, estimated glomerular filtration rate; HCM, hypertrophic cardiomyopathy; and LA, left atrium.

**Direct oral anticoagulants**

DOACs were developed to address the disadvantages of warfarin and are currently recommended as the first-line therapy over warfarin in patients with AF (except moderate to severe mitral stenosis or mechanical heart valve recipients) in this guideline. All 4 pivotal clinical trials comparing individual DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) with warfarin showed superiority or noninferiority to warfarin for the prevention of stroke or systemic embolism in patients with AF except for moderate to severe mitral stenosis or mechanical heart valve.<sup>2–5</sup> They also showed significantly lower risks of major bleeding in the apixaban, dabigatran 110 mg twice daily group, and edoxaban 30 mg or 60 mg daily dose groups compared with the warfarin group or nonsignificant differences in major bleeding between dabigatran 150 mg twice daily group or the rivaroxaban group and warfarin. All DOAC groups showed significantly lower risks of intracranial hemorrhage (ICH) compared with warfarin. Gastrointestinal bleeding risks were significantly higher in the dabigatran 150 mg twice daily, edoxaban 60 mg once daily, and rivaroxaban groups compared with the warfarin group. However, the apixaban group did not significantly increase the risk of gastrointestinal bleeding compared with the warfarin group.

**6.3.1. Antithrombotic Therapy**

Recommendations for Antithrombotic Therapy Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	A	1. For patients with AF and an estimated annual thromboembolic risk of ≥2% per year (eg, CHA <sub>2</sub> DS <sub>2</sub> -VASc score of ≥2 in men and ≥3 in women), anticoagulation is recommended to prevent stroke and systemic thromboembolism. <sup>1–7</sup>
1	A	2. In patients with AF who do not have a history of moderate to severe rheumatic mitral stenosis or a mechanical heart valve, and who are candidates for anticoagulation, DOACs are recommended over warfarin to reduce the risk of mortality, stroke, systemic embolism, and ICH. <sup>1–7</sup>
2a	A	3. For patients with AF and an estimated annual thromboembolic risk of ≥1% but <2% per year (equivalent to CHA <sub>2</sub> DS <sub>2</sub> -VASc score of 1 in men and 2 in women), anticoagulation is reasonable to prevent stroke and systemic thromboembolism. <sup>1,3</sup>
3: Harm	B-R	4. In patients with AF who are candidates for anticoagulation and without an indication for antiplatelet therapy, aspirin either alone or in combination with clopidogrel as an alternative to anticoagulation is not recommended to reduce stroke risk. <sup>8,9</sup>
3: No Benefit	B-NR	5. In patients with AF without risk factors for stroke, aspirin monotherapy for prevention of thromboembolic events is of no benefit. <sup>10,11</sup>

**Synopsis**

A high risk for stroke or systemic embolism is about 2% per year, and all the DOAC trials (Re-LY [Randomized Evaluation of Long-Term Anticoagulation Therapy]; ROCKET AF [Rivaroxaban Once Daily Oral Direct

**Table 12. Thromboembolic Event Rates by Point Score for ATRIA, CHADS<sub>2</sub>, and CHA<sub>2</sub>DS<sub>2</sub>-VASc Risk Scores\***

ATRIA				CHADS <sub>2</sub> †			CHA <sub>2</sub> DS <sub>2</sub> -VASc‡		
Points	Events	Person-Years	Rate per 100 Person-Years	Events	Person-Years	Rate per 100 Person-Years	Events	Person-Years	Rate per 100 Person-Years
0	2	2652	0.08	22	6126	0.36	1	2493	0.04
1	12	2819	0.43	121	10084	1.20	21	3806	0.55
2	14	1419	0.99	253	9757	2.59	46	5560	0.83
3	13	1780	0.73	178	4782	3.72	121	7305	1.66
4	19	2960	0.64	81	1309	6.19	193	6898	2.80
5	36	3614	0.99	19	450	4.23	175	4057	4.31
6	83	4346	1.91	11	101	10.84	85	1783	4.77
7	119	4768	2.50	–	–	–	24	498	4.82
8	151	3913	3.86	–	–	–	14	179	7.82
9	104	2400	4.33	–	–	–	5	30	16.62
10	75	1181	6.35	–	–	–	–	–	–
11	31	501	6.18	–	–	–	–	–	–
12	20	183	10.95	–	–	–	–	–	–
13	4	53	7.52	–	–	–	–	–	–
14	2	12	16.36	–	–	–	–	–	–
15	0	7	0	–	–	–	–	–	–
All	685	32 609	2.10	–	–	–	–	–	–

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\*Black lines identify thresholds for low-, moderate-, and high-risk categories for the 3 stroke risk point scores using published cut points.<sup>8,9</sup>

†The CHADS<sub>2</sub> score assigns points as follows: 1 point each for the presence of congestive heart failure, hypertension, age ≥75 y, and diabetes mellitus and 2 points for history of stroke/transient ischemic attack.

‡The CHA<sub>2</sub>DS<sub>2</sub>-VASc score assigns points as follows: 1 point each for congestive heart failure/left ventricular dysfunction, hypertension, diabetes mellitus, vascular disease, age 65 to 74 y, and female sex, and 2 points each for age ≥75 y and stroke/transient ischemic attack/thromboembolism.

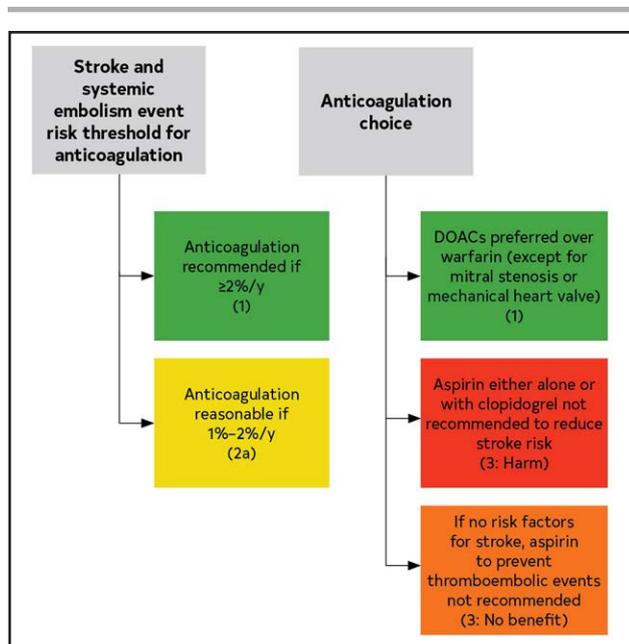
ATRIA indicates Anticoagulation and Risk Factors in Atrial Fibrillation; anemia, renal disease, elderly (age ≥75 y), any previous bleeding, hypertension; CHADS<sub>2</sub>, congestive heart failure, hypertension, age >75 y, diabetes, stroke/transient ischemia attack/thromboembolism; and CHA<sub>2</sub>DS<sub>2</sub>-VASc, indicates congestive heart failure, hypertension, age ≥75 y (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 y, sex category.

Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation]; ARISTOTLE; and ENGAGE AF-TIMI 48 [Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48]) included patients with this level of risk.<sup>1–4</sup> Patients at intermediate risk (1%–2%/y) can also benefit from anticoagulation, and the RE-LY<sup>1</sup> and ARISTOTLE<sup>3</sup> trials included this population. Stroke risk scores applied to cohorts give different stroke rates, and therefore any score should be viewed as only an estimate of true risk; in addition some scores used stroke, while others used thromboembolic events. Nonetheless, it is practical to use a validated risk score, such as CHA<sub>2</sub>DS<sub>2</sub>-VASc, ATRIA, or GARFIELD-AF. Future research may yield improved risk scores that refine how to incorporate risk modifiers, such as female sex<sup>12</sup> and other parameters such as AF burden. Anticoagulation has also been shown to be superior to antiplatelet therapy to reduce stroke risk.<sup>8,9</sup> Recommendations for

antithrombotic selection in valvular heart disease (VHD) are provided in **Section 6.8.5 (“AF in VHD”)** and for AFL in **Section 6.8.6** (Figure 10).

### Recommendation-Specific Supportive Text

1. Randomized trials published in the 1990s established the superiority of anticoagulation, at that time limited to warfarin, to reduce stroke.<sup>11</sup> Since that time, management has advanced considerably, and the randomized trials that compared DOACs with warfarin<sup>1–4</sup> are more relevant to current antithrombotic management. In these trials<sup>1–4</sup> and meta-analyses,<sup>5–7</sup> DOACs were favored for lower risk of stroke, systemic embolism, and ICH.<sup>1–7</sup> These trials reported the CHADS<sub>2</sub> score. The recently studied ATRIA and Swedish cohorts<sup>13,14</sup> reported lower stroke rates, by CHADS<sub>2</sub> score, compared with that previously reported.<sup>15</sup> A CHADS<sub>2</sub> score of 1 gave a stroke rate of 1.20 in ATRIA<sup>14</sup> and 2.4 in a Swedish cohort.<sup>13</sup> A CHADS<sub>2</sub> score of 2



**Figure 10. Antithrombotic Options in Patients With AF.**

Colors correspond to Table 2. AF indicates atrial fibrillation; and DOAC, direct oral anticoagulant.

gave a stroke rate of 2.59 in ATRIA<sup>14</sup> and 3.5 in the Swedish cohort.<sup>13</sup> Therefore, the stroke risk of patients in the rivaroxaban<sup>2</sup> and edoxaban<sup>4</sup> trials was likely  $>2\%$  given a required minimum CHADS<sub>2</sub> score of 2, and lower in the apixaban<sup>3</sup> and dabigatran<sup>1</sup> trials that included scores of 0 and 1. A Markov state transition decision model<sup>16</sup> concluded that anticoagulation was preferred for a stroke rate of 1.7%. Therefore, a stroke and systemic embolism risk threshold of 2% is likely to yield a benefit that far exceeds risk. In some conditions, such as hypertrophic cardiomyopathy, the risk of stroke is high enough independent of risk score to indicate anticoagulation.<sup>17</sup>

2. In the randomized DOAC trials, all DOACs achieved noninferiority<sup>1-4</sup> and in 2 trials (for dabigatran, RE-LY, and for apixaban, ARISTOTLE) were superior to warfarin. With warfarin, regular assessment of the INR is necessary to maintain a therapeutic value. In the RCTs, the mean time in therapeutic range was only 55% in ROCKET AF<sup>2</sup> and highest at 66% in ARISTOTLE.<sup>3</sup> In a meta-analysis,<sup>6</sup> DOACs, compared with warfarin, had a relative risk of stroke of 0.81 (95% CI, 0.73-0.91;  $P<0.0001$ ), a relative risk of mortality of 0.90 (95% CI, 0.85-0.95;  $P=0.0003$ ), relative risk of ICH of 0.48 (95% CI, 0.39-0.59;  $P<0.0001$ ), and increased relative risk of bleeding of 1.25 (95% CI, 1.01-1.55;  $P=0.043$ ). Although patients with moderate to severe mitral stenosis or mechanical valve were excluded from DOAC trials (and

subsequently shown they may have worse outcomes with DOACs), other forms of VHD were allowed, such as aortic stenosis or regurgitation or mitral regurgitation. Bioprosthetic valves and valve repair were allowed in the edoxaban (ENGAGE AF) and apixaban (ARISTOTLE) trials, and valve repair in the rivaroxaban (ROCKET AF) trial. A systematic review<sup>18</sup> of patients with VHD (other than mitral stenosis or mechanical valve) concluded that DOACs were safe.

3. As the DOAC trials<sup>1-4</sup> demonstrated improved safety compared with warfarin, the threshold of using a DOAC might be different than for warfarin.<sup>16</sup> A Markov decision model found the tipping point for warfarin to be at 1.7%/year stroke risk.<sup>16</sup> Considering the improved ICH and mortality risk of DOACs compared with warfarin in meta-analyses of the DOAC trials,<sup>5-7</sup> it is appropriate to designate a lower stroke risk threshold if a DOAC is utilized. The dabigatran<sup>1</sup> and apixaban<sup>3</sup> trials included lower risk patients and about one-third of patients had a CHADS<sub>2</sub> score of 0 or 1. This likely corresponds to an estimated annual stroke risk of about 1%, considering more recent cohorts.<sup>13,14</sup> This is further supported by meta-analyses that showed a consistent benefit of DOACs across a broad range of vulnerable patients, including as classified by CHADS<sub>2</sub> scores.<sup>6,7</sup>
4. A meta-analysis of AF trials from the 1990s and early 2000s found that while antiplatelet therapy (APT), most commonly aspirin, reduced stroke and systemic embolism compared with placebo, APT was inferior to warfarin in patients with AF.<sup>11</sup> Aspirin was studied compared to apixaban in the AVERROES trial (Apixaban Versus ASA to Prevent Stroke In AF Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment)<sup>9</sup> for patients unsuitable for VKAs; this trial was stopped early due to the benefit of apixaban over aspirin to prevent stroke or systemic embolism, while major bleeding was similar between the 2 arms. The combination of clopidogrel and aspirin was compared to VKAs in ACTIVEW (Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events),<sup>8</sup> and this trial was stopped prematurely due to the superiority of anticoagulation with VKAs to prevent stroke, non-central nervous system systemic embolus, MI, or vascular death. Unless there is an indication for antiplatelet therapy, such as coronary artery disease (CAD) or vascular disease, patients with AF should not be prescribed antiplatelet therapy to reduce stroke risk.

5. Aspirin therapy was compared with no treatment in patients with low stroke risk in a multicenter RCT in Japan, the Japan Atrial Fibrillation Stroke Trial.<sup>10</sup> This trial was stopped early when an interim analysis showed that aspirin gave a marginally higher risk of major bleeding and was unlikely to prevent primary or secondary endpoints. The primary endpoint was noncardiovascular death, ICH, major bleeding, and peripheral embolization. A meta-analysis of 7 trials that studied aspirin versus placebo found that aspirin reduced stroke by 19%, which did not reach statistical significance with a CI that included 0 (−1% to 35%). Four of these were primary prevention trials and showed an absolute risk reduction with aspirin of 0.8% per year, with a number needed to treat of 125.<sup>11</sup> Although aspirin has not been studied in patients without any risk factors for stroke, patients without stroke risk may derive no benefit from aspirin therapy. In fact, 1 study that analyzed stroke mechanisms in the SPAF (Stroke Prevention in Atrial Fibrillation) I-III trials demonstrated that aspirin did not decrease the rate of cardioembolic stroke and that AF patients at highest risk for stroke are those with the highest rates of cardioembolic stroke and have the greatest reduction in stroke with anticoagulants.<sup>19</sup> Thus, modest reduction in stroke observed in some trials may have been related to noncardioembolic stroke in patients with additional risk factors.

### 6.3.1.1. Considerations in Managing Anticoagulants

Recommendations for Considerations in Managing Anticoagulants Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	C-LD	1. For patients with AF receiving DOACs, optimal management of drug interactions is recommended for those receiving concomitant therapy with interacting drugs, especially CYP3A4 and/or p-glycoprotein inhibitors or inducers (Table 13). <sup>1-7</sup>
1	B-R	2. For patients with AF receiving warfarin, <sup>†</sup> a target INR between 2 and 3 is recommended, as well as optimal management of drug-drug interactions, consistency in vitamin K dietary intake, and routine INR monitoring to improve time in therapeutic range and to minimize risks of preventable thromboembolism or major bleeding. <sup>8-10</sup>
3: Harm	B-NR	3. For patients with AF, nonevidence-based doses of DOACs should be avoided to minimize risks of preventable thromboembolism or major bleeding and to improve survival. <sup>11,12</sup>

<sup>†</sup>Excludes patients with mechanical valves.

### Synopsis

Multiple factors need to be considered to select an optimal OAC in patients with AF. Efficacy, safety, insurance coverage, renal/hepatic function, drug interaction screening, medication adherence, and patient preferences are the major factors for consideration.

Dosing of DOACs in patients with AF should be selected based on age, renal function, weight, and concomitant medications. The hepatic function also needs to be evaluated for the appropriateness of DOACs. Characteristics and dosing of OACs are summarized in Table 13. Although DOAC drug interactions occur in practice less frequently than with warfarin, clinically significant drug interactions through CYP3A4 and/or p-glycoprotein should be carefully evaluated. Strong CYP3A4 and/or p-glycoprotein inhibitors such as ketoconazole, itraconazole, and ritonavir may significantly increase DOAC plasma levels and the risk of bleeding, while strong CYP3A4 and/or p-glycoprotein inducers such as rifampin, phenytoin, phenobarbital, primidone, carbamazepine, or St. John's wort may lower DOAC plasma levels and increase the risks of stroke or systemic embolism. The routine measurement of DOAC plasma concentrations is not indicated in practice due to the lack of well-established therapeutic ranges in the literature. DOAC levels may be indicated when clinicians assess DOAC adherence for potentially non-compliant patients, quantify residual anticoagulation levels before emergency invasive procedures/surgeries, or evaluate the absorption of DOAC after bariatric surgery. Regular monitoring is recommended to optimize indications, ensure appropriate dosing, and avoid adverse effects. Suggested laboratory monitoring is summarized in Figure 11.

If warfarin is selected over DOACs, achievement of higher time in therapeutic range (eg,  $\geq 70\%$ ), and thorough consideration of drug-drug interactions, vitamin K food intake advice, and patient education on adherence to dosing instructions are important to reduce adverse effects.

### Recommendation-Specific Supportive Text

1. Rivaroxaban is contraindicated for patients receiving ketoconazole or ritonavir, because ketoconazole or ritonavir coadministration significantly increased rivaroxaban plasma levels by 158% or 153%, respectively.<sup>1</sup> Apixaban also requires dose adjustment to 2.5 mg twice daily for patients receiving apixaban 5 mg twice daily when ketoconazole, itraconazole, or ritonavir is started.<sup>13</sup> Apixaban plasma level was significantly increased by 99% when ketoconazole was coadministered in healthy subjects.<sup>2</sup> The concomitant therapy of dronedarone or ketoconazole for patients with creatinine clearance (CrCl) 30 to 50 mL/min receiving dabigatran requires dose adjustment to dabigatran 75 mg twice daily because it produced comparable dabigatran exposure in patients with CrCl 30 to 50 mL/min receiving the concomitant therapy to patients with CrCl 15 to 29 mL/min receiving only dabigatran.<sup>14</sup> A retrospective study revealed that the probability of patients with

**Table 13. OACs Pharmacokinetic Characteristics and Dosing**

Class	VKA	Direct Thrombin Inhibitor		Factor Xa Inhibitor					
Name	Warfarin	Dabigatran		Rivaroxaban		Apixaban		Edoxaban	
Metabolism	S-isomer: CYP2C9 R-isomer: CYP1A2, CYP2C19, CYP3A4	Minimal		CYP3A4/5		CYP3A4		Minimal CYP3A4	
P-glycoprotein substrate	No	Yes		Yes		Yes		Yes	
Excretion	0% renal; very little warfarin excreted unchanged in urine	80% renal		66% renal, 28% feces		27% renal, 73% biliary and intestinal		50% renal, 50% liver and biliary/intestinal	
Half-life	20-60 h	12-17 h		5-9 h		12 h		10-14 h	
Renal dosing adjustment based on actual body weight	N/A	CrCl >30 mL/min	150 mg twice daily	CrCl >50 mL/min	20 mg daily with the biggest meal*		5 mg twice daily	CrCl >50–≤95 mL/min	60 mg once daily
		CrCl 15-30 mL/min	75 mg twice daily	CrCl 15-50 mL/min	15 mg daily with the biggest meal*	If any 2 of the following: age ≥80y, body weight ≤60 kg, SCr ≥1.5 mg/dL	2.5 mg twice daily	CrCl 15-50 mL/min	30 mg once daily
Drug interaction management based on concomitant therapy of CYP3A4 inhibitors/ p-glycoprotein inhibitors	Adjust dose based on INR trends	CrCl 30-50 mL/min with concomitant use of dronedarone or systemic ketoconazole: 75 mg twice daily CrCl <30 mL/min: avoid dabigatran use concomitantly with dronedarone or systemic ketoconazole		Avoid rivaroxaban use with concomitant therapy of combined p-glycoprotein and strong CYP3A4 inhibitors (eg, systemic ketoconazole and ritonavir) No dose adjustment required with clarithromycin Avoid rivaroxaban use in patients with CrCl 15–<80 mL/min receiving combined p-glycoprotein and moderate CYP3A4 inhibitors (eg, erythromycin)		In patients receiving apixaban 5 mg twice daily, reduce dose to 2.5 mg twice daily when combined p-glycoprotein and strong CYP3A4 inhibitors (eg, itraconazole, systemic ketoconazole, ritonavir) are used concomitantly If patients already receiving apixaban 2.5 mg twice daily, avoid apixaban use if combined p-glycoprotein and strong CYP3A4 inhibitors are concomitantly used		No dose adjustment is required	
Drug interaction management based on concomitant therapy of p-glycoprotein/ CYP3A4 inducers (eg, carbamazepine, phenytoin, rifampin, St. John's wort)	Adjust dose based on INR trends	Avoid use		Avoid use		Avoid use		Avoid use with rifampin. No study evaluated the effect of other p-glycoprotein/CYP3A4 inducers on edoxaban drug levels	

(Continued)

**Table 13. Continued**

Class	VKA	Direct Thrombin Inhibitor	Factor Xa Inhibitor		
	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Appropriate use based on liver function (Child-Pugh score) <sup>†</sup> Child-Pugh A (mild)	Not mentioned in the labeling	No dose adjustment needed			
Child-Pugh B (moderate)		Use with caution	Avoid use	Use with caution	Use with caution
Child-Pugh C (severe)		Avoid use	Avoid use	Avoid use	Avoid use

Information obtained from manufacturer package inserts.<sup>13,14,20–22</sup> Adapted with permission from pgs. 28–31 of Kido et al.<sup>23</sup> Copyright 2021 American College of Clinical Pharmacy.

\*The effect of food (high-fat, high-calorie meal) on bioavailability for 10- and 20-mg tablet was evaluated in 24 subjects under fed and fasting conditions. After a single oral 20-mg dose, area under the curve was increased by 39%, and C<sub>max</sub> was increased by 76% under fed condition, but area under the curve and C<sub>max</sub> were similar between fasting and fed conditions.<sup>19</sup>

<sup>†</sup>Child-Pugh scoring: the severity of liver disease, primarily cirrhosis. Child-Pugh A (mild): 5 to 6 points; Child-Pugh B (moderate): 7 to 9 points; Child-Pugh C (severe): 10 to 15 points. The score is based on the 5 variables: encephalopathy (none=1 point, grade 1 and 2=2 points, grade 3 and 4=3 points); ascites (none=1 point, slight=2 points, moderate=3 points); total bilirubin (<2 mg/mL=1 point, 2–3 mg/mL=2 points, >3 mg/mL=3 points); albumin (>3.5 mg/mL=1 point, 2.8–3.5 mg/mL=2 points, <2.8 mg/mL=3 points); INR (<1.7=1 point, 1.7–2.2=2 points, >2.2=3 points).

CrCl indicates creatinine clearance; INR, international normalized ratio; OAC, oral anticoagulant; Scr, serum creatinine; and VKA, vitamin K antagonist.

subreference DOAC levels was significantly higher in patients receiving antiepileptic drugs compared to those not receiving any CYP3A4 inducers.<sup>4</sup> The claim-based retrospective cohort study showed that CYP-inducing antiepileptic drug use was significantly associated with an 86% increase in thromboembolic and ischemic adverse events in patients receiving DOACs.<sup>6</sup> A prospective multicenter cohort study corroborated that the patients receiving concomitant therapy of DOACs and antiepileptic drugs developed a higher rate of stroke/TIA/systemic embolism (5.7% patient-year).<sup>7</sup>

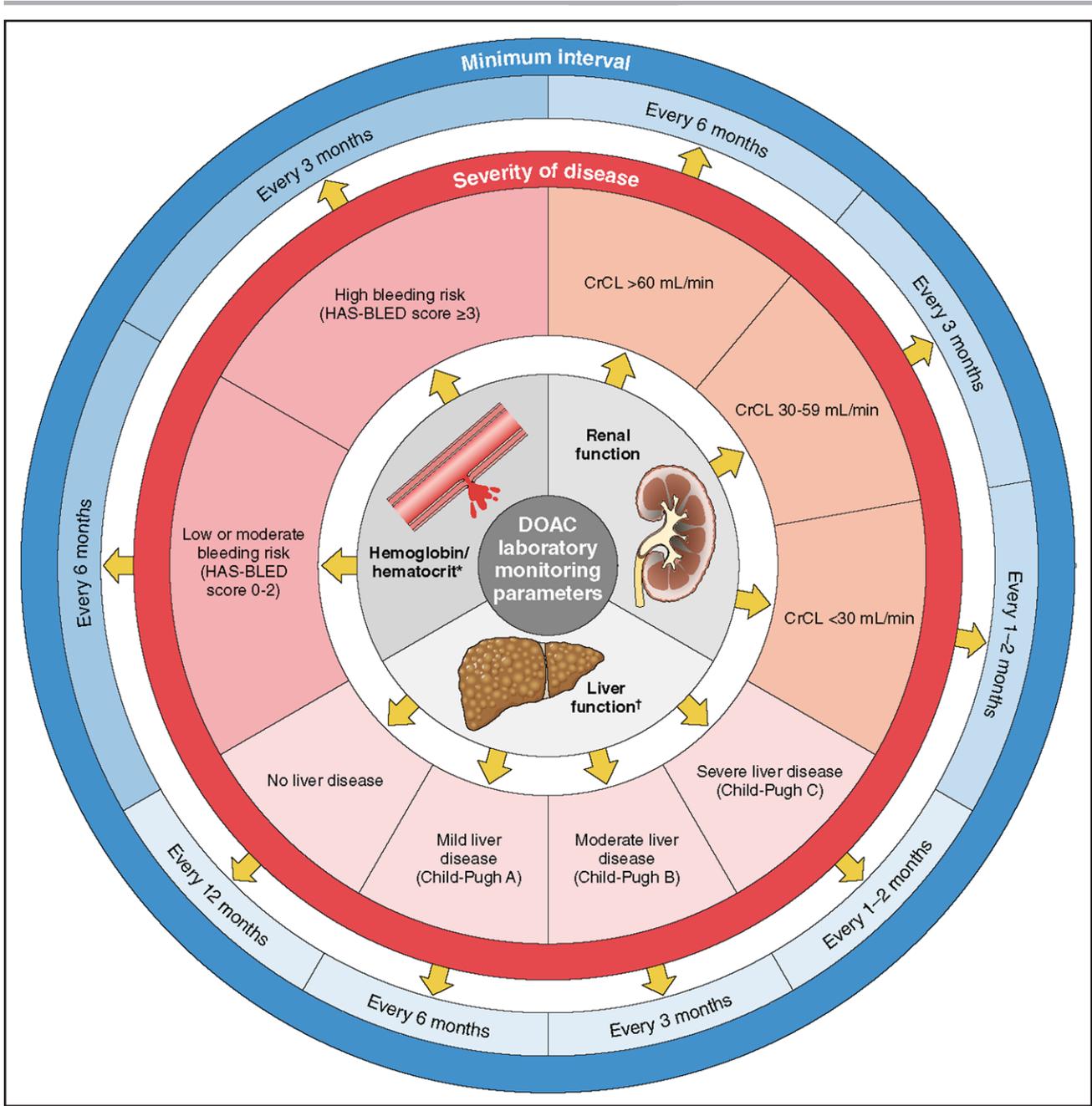
- Warfarin remains the preferred agent in patients with AF receiving CYP3A4/p-glycoprotein-inducing agents, or moderate-severe mitral stenosis or mechanical heart valve. Also, warfarin may be selected over DOACs in patients with AF due to higher cost or intolerances of DOACs. The optimal INR control, with a therapeutic INR goal of 2 to 3, needs to be achieved through the appropriate drug-drug interaction management, vitamin K dietary education, and routine INR monitoring. A systematic review of 47 studies found that time in therapeutic INR range showed negative correlation with risks of thromboembolism (R, -0.59; *P*=0.01) and major bleeding (R, -0.59; *P*=0.002).<sup>8</sup> An RCT revealed that a weekly vitamin K dietary modification significantly achieved a therapeutic INR more frequently than a conventional group (74 versus 58%; *P*=0.04) at 90 days after randomization.<sup>9</sup> A meta-analysis of 11 RCTs and 61 observational studies for warfarin drug interactions found that the concomitant use of APT (odds ratio [OR], 1.74 [95% CI, 1.56–1.94]), nonsteroidal anti-inflammatory drugs (OR, 1.83 [95% CI, 1.29–2.59]), selective serotonin reuptake inhibitors (OR, 1.62 [95% CI, 1.42–1.85]), or antimicrobial agents (OR, 1.63 [95% CI, 1.45–1.83]) was significantly associated with higher risks of clinically relevant bleeding.<sup>10</sup>

- A significant number of patients with nonvalvular AF are receiving DOAC off-label doses not compliant with labeling.<sup>15–18</sup> A meta-analysis of cohort studies showed that inappropriately lower DOAC doses are significantly associated with higher stroke or systemic embolism risks compared with the standard labeled doses (OR, 1.21 [95% CI, 1.02–1.43]; *P*=0.03), but no significant differences in bleeding risks were observed (OR, 1.03 [95% CI, 0.92–1.15]; *P*=0.62).<sup>11</sup> Of note, 9 of 16 included studies were performed in Asia, while 4 studies in the United States, 2 studies in Europe, and 1 worldwide study were included. Another meta-analysis of observational studies found that inappropriately higher DOAC doses were significantly associated with higher risks of ischemic stroke/systemic embolism (hazard ratio [HR], 1.26 [95% CI, 1.11–1.43]; *P*=0.003) or major bleeding (HR, 1.30 [95% CI, 1.04–1.62]; *P*=0.025) compared with the standard doses.<sup>12</sup> In this study, underdosing was also associated with a higher risk of net clinical outcome (HR, 1.19 [95% CI, 1.04–1.40]; *P*=0.04) and all-cause death (HR, 1.24 [95% CI, 1.04–1.48]; *P*=0.02). Off-label dosing should be avoided to optimize the efficacy and safety of DOACs.

#### 6.4. Silent AF and Stroke of Undetermined Cause

**Recommendation for Silent AF and Stroke of Undetermined Cause**  
Referenced studies that support the recommendation are summarized in the [Online Data Supplement](#).

COR	LOE	Recommendation
2a	B-R	1. In patients with stroke or TIA of undetermined cause, initial cardiac monitoring and, if needed, extended monitoring with an implantable loop recorder are reasonable to improve detection of AF. <sup>1</sup>



**Figure 11. DOAC Laboratory Monitoring.**

\*HAS-BLED scoring (low risk=score 0, moderate risk=score 1-2, high risk=score ≥3): uncontrolled hypertension (systolic blood pressure >160 mm Hg)=1 point; abnormal renal (serum creatinine >2.26 mg/dL, dialysis, or kidney transplant) or hepatic function (bilirubin >2 times upper limit normal, alanine aminotransferase/aspartate aminotransferase/alkaline phosphatase >3 times upper limit normal, or cirrhosis)=1 or 2 points; stroke (hemorrhagic or ischemic)=1 point; bleeding history or predisposition=1 point; labile INR (time in therapeutic range <60%)=1 point; elderly age ≥65 years=1 point; drugs (antiplatelet agents or nonsteroidal anti-inflammatory drugs) or excessive alcohol intake (8 units/week)=1 or 2 points. †Child-Pugh scoring: the severity of liver disease, primarily cirrhosis in patients with documented liver disease. Child-Pugh A (mild): 5 to 6 points; Child-Pugh B (moderate): 7 to 9 points; Child-Pugh C (severe): 10 to 15 points. The score is based on the 5 variables: encephalopathy (none=1 point, grade 1 and 2=2 points, grade 3 and 4=3 points); ascites (none=1 point, slight=2 points, moderate=3 points); total bilirubin (<2 mg/mL=1 point, 2-3 mg/mL=2 points, >3 mg/mL=3 points); albumin (>3.5 mg/mL=1 point, 2.8-3.5 mg/mL=2 points, <2.8 mg/mL=3 points); INR (<1.7=1 point, 1.7-2.2=2 points, >2.2=3 points). *Original figure created by the 2023 Atrial Fibrillation Guideline Writing Committee.* CrCL indicates creatinine clearance based on actual body weight; DOAC, direct oral anticoagulant; and INR, international normalized ratio.

### Synopsis

Approximately 25% to 30% of ischemic strokes remain cryptogenic after standard stroke evaluation.<sup>2,3</sup> A large proportion of these events are presumed to be related to occult AF, particularly those of embolic appearance.<sup>4,5</sup> APT is the recommended treatment of choice for patients with cryptogenic stroke, including embolic stroke of undetermined source.<sup>6,7</sup> For patients with AF in general, however, anticoagulation has been shown to be superior to APT for stroke risk reduction.<sup>8</sup> Thus, detection of occult AF after stroke may have significant therapeutic implications. Randomized trials have shown longer durations of cardiac monitoring result in higher rates of AF detection after stroke.<sup>1,9,10</sup> However, data are limited regarding the effects of extended monitoring on risk reduction of recurrent stroke or poststroke mortality. For recommendations on anticoagulation and risk factors, refer to **Section 6.4.1 (“Oral Anticoagulants”).**

### Recommendation-Specific Supportive Text

1. Growing evidence supports the use of extended cardiac monitoring for the identification of occult AF in patients with cryptogenic stroke.<sup>11,12</sup> In the EMBRACE (30 Day Event Monitoring Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event) trial, which randomized 572 patients  $\geq 55$  years of age with recent cryptogenic stroke or TIA to either 30-day external loop recorder or conventional 24-hour Holter monitoring, extended monitoring was associated with higher rates of AF detection at 90 days.<sup>1</sup> The CRYSTAL-AF (Cryptogenic Stroke and Underlying AF) trial randomized 441 patients  $\geq 40$  years of age with recent cryptogenic stroke or TIA to cardiac monitoring with either insertable loop recorder or conventional follow-up ECGs. Implantable recorder was superior in detecting AF at 6 months (8.9% versus 1.4%), 12 months (12.4% versus 2.0%), and 3 years (30% versus 3%).<sup>9</sup> In FIND-AF (Future Innovations in Novel Detection of Atrial Fibrillation), which compared repeated sets of 10-day Holter monitoring (at baseline, 3-month, and 6-month timepoints) to conventional 24-Holter in patients  $\geq 60$  years of age with recent stroke, higher rates of detection were associated with repeated monitoring (14% versus 5%; absolute difference, 9.0% [95% CI, 3.4-14.5];  $P=0.002$ ).<sup>10</sup> Finally, the PER DIEM (Post-Embolitic Rhythm Detection with Implantable vs External Monitoring) RCT also showed a significantly greater proportion of patients with AF detected at 1 year with prolonged monitoring.<sup>13</sup> Additional studies are needed, however, to determine whether extended cardiac monitoring improves long-term poststroke outcomes.

### 6.4.1. Oral Anticoagulation for Device-Detected Atrial High-Rate Episodes Among Patients Without a Previous Diagnosis of AF

**Recommendations for Oral Anticoagulation for Device-Detected Atrial High-Rate Episodes Among Patients Without a Previous Diagnosis of AF**  
Referenced studies that support the recommendations are summarized in the [Online Data Supplement](#).

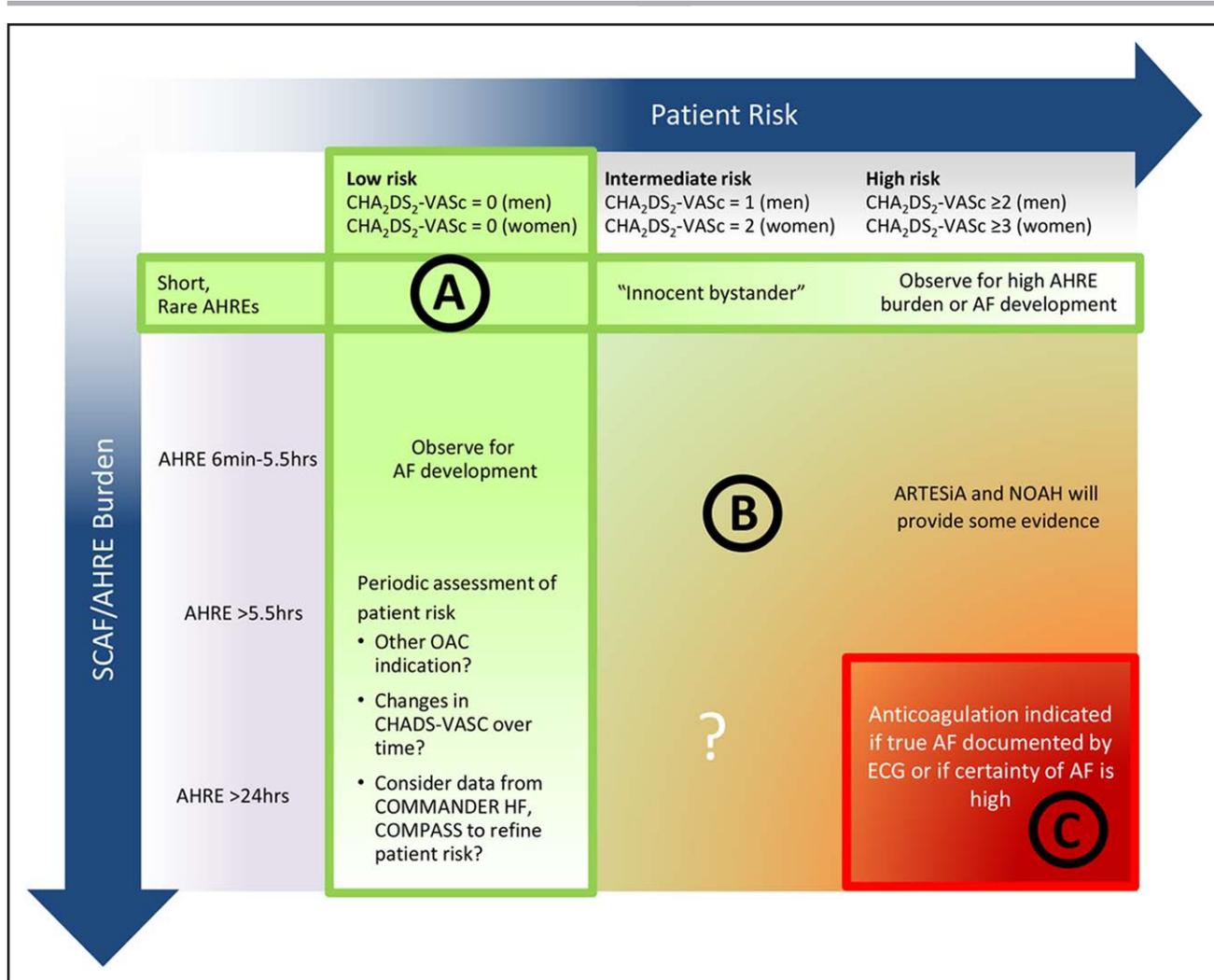
COR	LOE	Recommendations
2a	B-NR	1. For patients with a device-detected atrial high-rate episode (AHRE) lasting $\geq 24$ hours <sup>1</sup> and with a CHA <sub>2</sub> DS <sub>2</sub> -VASc score $\geq 2$ or equivalent stroke risk, <sup>2</sup> it is reasonable to initiate oral anticoagulation <sup>3</sup> within a SDM framework that considers episode duration and individual patient risk.
2b	B-NR	2. For patients with a device-detected AHRE lasting between 5 minutes and 24 hours and with a CHA <sub>2</sub> DS <sub>2</sub> -VASc score $\geq 3$ or equivalent stroke risk, <sup>2</sup> it may be reasonable to initiate anticoagulation within a SDM framework that considers episode duration and individual patient risk.
3: No Benefit	B-NR	3. Patients with a device-detected AHRE lasting $< 5$ minutes and without another indication for oral anticoagulation should not receive oral anticoagulation. <sup>4,5</sup>

### Synopsis

AHREs detected by a cardiovascular implantable electronic device are associated with a stroke risk lower than that of clinical AF<sup>6</sup> that varies according to the episode duration<sup>1</sup> and CHA<sub>2</sub>DS<sub>2</sub>-VASc score.<sup>2</sup> Clinician confirmation of the duration and nature of the longest atrial high-rate episode is recommended.<sup>1</sup> Episodes lasting  $\geq 24$  hours are associated with a significant risk of stroke or systemic embolism<sup>1,7</sup> that may be reduced with oral anticoagulation.<sup>3</sup> By contrast, short episodes, commonly defined as  $< 5$  minutes, are not associated with clinical events.<sup>4,5</sup> Patients with episodes of intermediate duration and with an elevated stroke risk may benefit from oral anticoagulation.<sup>2</sup> There is an interaction between AHRE duration and CHA<sub>2</sub>DS<sub>2</sub>-VASc score,<sup>2</sup> suggesting both may be used to guide oral anticoagulation candidacy (Figure 12). Of note, the threshold for anticoagulation is higher as in device-detected AF the risk of stroke may be lower than in clinical AF.

### Recommendation-Specific Supportive Text

1. AHREs lasting  $\geq 24$  hours are associated with an elevated risk of stroke that varies according to CHA<sub>2</sub>DS<sub>2</sub>-VASc score. AHRE burden is most commonly defined according to the duration of the longest-detected episode, though cumulative duration has also been examined. In a secondary analysis of the ASSERT (Atrial Fibrillation Reduction Atrial Pacing Trial), adjudicated AHREs  $> 24$  hours was associated with an increased risk of subsequent stroke or systemic embolism (adjusted HR, 3.24 [95% CI, 1.51-6.95];  $P=0.003$ ).<sup>1</sup> Similar findings are seen in observational studies in which most AHREs



**Figure 12. Consideration of Oral Anticoagulation for Device-Detected AHREs According to Patient Stroke Risk by CHA<sub>2</sub>DS<sub>2</sub>-VASc Score and Episode Duration.**

A potential approach to patients with SCAF could consider both patient risk (as gauged by the CHA<sub>2</sub>DS<sub>2</sub>-VASc score) and SCAF burden/duration. Circle A indicates patients at low risk or with short and infrequent AHREs do not require anticoagulation; Circle B, patients with intermediate risk and AHREs lasting >6 min to 24 h are an uncertain population but are currently under study in 2 prospective randomized controlled trials; and Circle C, patients at high risk with longer episodes could be considered reasonable candidates for anticoagulation, although the precise threshold for SCAF duration remains uncertain. Reproduced with permission from Noseworthy et al.<sup>13</sup> Copyright 2019 American Heart Association, Inc. Modified from Freedman et al.<sup>14</sup> Copyright 2017 Springer Nature Limited. AF indicates atrial fibrillation; AHRE, atrial high-rate episode; ARTESiA, Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Subclinical Atrial Fibrillation trial; COMMANDER HF, A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants With Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; ECG, electrocardiogram; NOAH, Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes Trial; OAC, oral anticoagulation; and SCAF, subclinical atrial fibrillation. Female sex is treated as a modifier in the computation of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score.

were not adjudicated,<sup>7</sup> though clinician confirmation is preferred. In an observational study linking administrative claims data<sup>2</sup> to a device database in which continuous rhythm monitoring data were available but not adjudicated, the risk of stroke among patients with subclinical AF >23.5 hours and a sex-modified CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥2 not taking anticoagulation exceeded 1% per year, a threshold that may be appropriate for use of non-VKAs, with a still higher stroke risk with increasing CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥3.<sup>8</sup> In a retrospective

cohort study of patients with subclinical AF >24 hours with an average CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 4.2±1.4, treatment of subclinical AF >24 hours with OAC was associated with a reduced stroke risk (HR, 0.28 [95% CI, 0.10-0.81]; P=0.02).<sup>2,3</sup>

2. Although the risk of stroke among patients with an AHRE of intermediate duration is lower than that among patients with an AHRE ≥24 hours, the precise stroke risk is uncertain and may vary according to the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. In ASSERT, AHREs lasting >6 minutes to 24 hours

were not associated with stroke or systemic embolism compared with patients without AHREs.<sup>1</sup> The CHA<sub>2</sub>DS<sub>2</sub>-VASc score of this subpopulation was 2.2±1.0 (mean±SD). In the aforementioned study linking administrative claims data to a device database in which continuous rhythm monitoring data were available, the risk of stroke and systemic embolism off anticoagulation exceeded 1% among patients with a sex-modified CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 3 to 4 and exceeded 2% among patients with a sex-modified CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥5.<sup>2</sup>

- Brief episodes of subclinical AF are at low risk of clinical events. In RATE (Registry of Atrial Tachycardia and Atrial Fibrillation), patients with clinical events such as hospitalization, death, or stroke were more likely than those without to have AHREs with either onset or offset of an adjudicated, single ECG (31.9% versus 22.1% among patients with pacemakers and 28.7% and 20.2% among patients with implantable cardioverter-defibrillators [ICDs]).<sup>4</sup> AHREs >5 minutes are highly correlated with AF and AFL, whereas shorter episodes often represent other tachyarrhythmias.<sup>9</sup> To remove most episodes of oversensing, AHREs lasting ≤5 minutes were excluded from analysis of MOST (Mode Selection Trial).<sup>10</sup> A similar threshold was used in several subsequent key studies to exclude spurious events.<sup>1,3,5,11,12</sup>

### 6.5. Nonpharmacological Stroke Prevention

Although oral anticoagulation is the standard of care to reduce the risk of ischemic stroke in patients with AF, it is contraindicated in some patients due to an excess risk of major bleeding. Surgical and percutaneous techniques to occlude the LAA have been developed to reduce the risk of ischemic stroke. These techniques have the potential to obviate the need for or supplement long-term oral anticoagulation in select patients. Surgical LAAO is a particularly important consideration in patients with AF who undergo cardiac surgery.

#### 6.5.1. Percutaneous Approaches to Occlude the LAA

Recommendations for Percutaneous Approaches to Occlude the LAA Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
2a	B-NR	1. In patients with AF, a moderate to high risk of stroke (CHA <sub>2</sub> DS <sub>2</sub> -VASc score ≥2), and a contraindication (Table 14) to long-term oral anticoagulation due to a nonreversible cause, percutaneous LAAO (pLAAO) is reasonable. <sup>1-4</sup>
2b	B-R	2. In patients with AF and a moderate to high risk of stroke and a high risk of major bleeding on oral anticoagulation, pLAAO may be a reasonable alternative to oral anticoagulation based on patient preference, with careful consideration of procedural risk and with the understanding that the evidence for oral anticoagulation is more extensive. <sup>1-3,5,6</sup>

### Synopsis

A large body of evidence supports the use of OACs to reduce the risk of ischemic stroke in patients with AF; however, OACs may be contraindicated in some patients (Table 14). pLAAO devices are designed to prevent embolization of LAA thrombi and potentially obviate the need for OAC for stroke risk reduction. RCTs have demonstrated pLAAO to be noninferior to warfarin and DOACs for stroke and systemic embolism with a reduced risk of major bleeding.<sup>1-4</sup> A prospective nonrandomized study has shown that patients deemed unsuitable for OAC who undergo pLAAO implant have a lower-than-expected risk of ischemic stroke.<sup>5</sup> Prospective registries of pLAAO device implant in patients who are not on long-term OAC have shown a high rate of procedural success, a low risk of major procedure-related complications, and a low rate of ischemic stroke in follow-up.<sup>6,7</sup> Based on these findings, pLAAO is reasonable in patients with nonvalvular AF who have a contraindication to long-term OAC due to a nonreversible cause. Additionally, pLAAO may be reasonable as an alternative to OAC based on patient preference after careful consideration of procedural risk and with the understanding that there is a much greater body of evidence supporting OAC in this population in general.

### Recommendation-Specific Supportive Text

- pLAAO has been evaluated in patients with AF and a contraindication to OAC. The ASAP (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology) study was a non-randomized trial evaluating the performance of the Watchman device in 150 patients with AF who were deemed ineligible for OAC with warfarin.<sup>5</sup> The rate of ischemic stroke was lower in patients who received the Watchman device than would be expected based on the CHADS<sub>2</sub> scores of the cohort (2.3% versus 7.3%). The EWOLUTION (Evaluating Real-Life Clinical Outcomes in Atrial Fibrillation Patients Receiving the WATCHMAN Left Atrial Appendage Closure Technology) prospective registry showed a high rate of Watchman device procedural success (98.5%) with a low ischemic stroke risk (1.1%). This low ischemic stroke was demonstrated despite most of the patients (73%) not using oral anticoagulation periprocedurally.<sup>6</sup> The PINNACLE FLX (Protection Against Embolism for Nonvalvular AF Patients: Investigational Device Evaluation of the Watchman FLX LAA Closure Technology) prospective registry of the next-generation Watchman FLX device showed a high rate of procedural success (98.8%) and a low rate (0.5%) of the primary safety endpoint (death, ischemic stroke, systemic embolism, procedure-related events requiring open cardiac

**Table 14. Situations in Which Long-Term Anticoagulation Is Contraindicated and Situations When It Remains Reasonable**

Long-Term Anticoagulation Contraindicated	Long-Term Anticoagulation Is Still Reasonable
Severe bleeding due to a nonreversible cause involving the gastrointestinal, pulmonary, or genitourinary systems	Bleeding involving the gastrointestinal, pulmonary, or genitourinary systems that is treatable
Spontaneous intracranial/intraspinal bleeding due to a nonreversible cause	Bleeding related to isolated trauma
Serious bleeding related to recurrent falls when cause of falls is not felt to be treatable	Bleeding related to procedural complications

surgery or major endovascular intervention).<sup>7</sup> Registry data have shown substantial variation in postprocedure antithrombotic regimens in real-world practice compared with protocols in the pivotal RCTs; the effect this has on long-term outcomes has not been clearly established.<sup>8</sup> ASAP-TOO (Assessment of the Watchman Device in Patients Unsuitable for Oral Anticoagulation) is an ongoing RCT evaluating the safety and efficacy of LAAO in patients with AF who are deemed ineligible for oral anticoagulation.<sup>9</sup>

- PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation) was a noninferiority RCT comparing pLAAO with the Watchman device with warfarin in patients with AF at an increased risk for stroke. pLAAO was noninferior to warfarin for both primary composite efficacy (stroke, systemic embolism, and cardiovascular/unexplained death) and safety (procedure-related events and major bleeding) endpoints.<sup>1</sup> pLAAO was superior to warfarin in terms of cardiovascular mortality (HR, 0.40, 95% CI, 0.21-0.75; *P*=0.005) and all-cause mortality (HR, 0.66, 95% CI, 0.45-0.98; *P*=0.004). The PREVAIL (Watchman Left Atrial Appendage Closure Device in Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy) study was a follow-up RCT that compared the Watchman device with warfarin in a similar patient population.<sup>2</sup> pLAAO did not achieve noninferiority for the first primary composite efficacy endpoint (stroke, systemic embolism, and cardiovascular/unexplained death) but was limited in statistical power because of unexpectedly low event rates. pLAAO was statistically noninferior to warfarin for nonprocedure-related strokes. Higher implant success and lower procedure-related safety event rates were observed in PREVAIL than PROTECT AF. A 5-year patient-level meta-analysis of these trials demonstrated similar efficacy of pLAAO for

stroke prevention and reduced rates of major bleeding compared with warfarin.<sup>3</sup> PRAGUE-17 (Left Atrial Appendage Closure vs Novel Anticoagulation Agents in Atrial Fibrillation) was an RCT that compared pLAAO with DOACs in patients with nonvalvular AF.<sup>4</sup> pLAAO was noninferior to DOACs for the combined safety and efficacy composite endpoint (stroke, TIA, systemic embolism, cardiovascular death, major or nonmajor clinically relevant bleeding, or procedure-/device-related complications).

**6.5.2. Cardiac Surgery—LAA Exclusion/Excision**

Recommendations for Cardiac Surgery—LAA Exclusion/Excision		
Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	A	1. In patients with AF undergoing cardiac surgery with a CHA <sub>2</sub> DS <sub>2</sub> -VASc score ≥2 or equivalent stroke risk, surgical LAA exclusion, in addition to continued anticoagulation, is indicated to reduce the risk of stroke and systemic embolism. <sup>1-3</sup>
1	A	2. In patients with AF undergoing cardiac surgery and LAA exclusion, a surgical technique resulting in absence of flow across the suture line and a stump of <1 cm as determined by intraoperative transesophageal echocardiography should be used. <sup>1,4,5</sup>
2b	A	3. In patients with AF undergoing cardiac surgery with CHA <sub>2</sub> DS <sub>2</sub> -VASc score ≥2 or equivalent stroke risk, the benefit of surgical LAA exclusion in the absence of continued anticoagulation to reduce the risk of stroke and systemic embolism is uncertain. <sup>1-3</sup>

**Synopsis**

Surgical left atrial appendage occlusion (S-LAAO) for reduction in the risk of recurrent arterial thromboemboli was first reported in 1949.<sup>6</sup> After decades of relative clinical equipoise,<sup>7,8</sup> accumulating evidence,<sup>2,8-10</sup> culminating in the large RCT LAAOS III (Left Atrial Appendage Occlusion Study),<sup>1</sup> supports a benefit of S-LAAO in patients with AF who undergo<sup>2,9</sup> coronary artery bypass graft surgery (CABG) or valve surgeries. A 2019 meta-analysis before the publication of LAAOS III reviewed 22 studies, including 280 585 patients of whom 36 686 underwent S-LAAO during cardiac surgery. S-LAAO showed an association with a 29% lower risk of stroke or thromboembolism. The all-cause mortality rate at 2 years was lower in patients who underwent S-LAAO. No benefit was found in the subgroup of studies that included patients without preoperative AF.<sup>9</sup> These favorable findings were validated by the 4770-subject LAAOS III, which confirmed S-LAAO in addition to OAC provides a 33% reduction in risk of stroke and systemic embolism.<sup>1</sup>

LAAOS III enrolled only patients with preexisting AF; evidence of the effectiveness of S-LAAO in patients without AF is inconsistent and suggests the benefit of

adjunctive S-LAAO is unclear in patients without preoperative AF.<sup>79</sup> The results of ongoing RCTs in this population are awaited.

### Recommendation-Specific Supportive Text

1. LAAOS III was performed with 4770 patients with AF and a CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  undergoing cardiac surgery randomized to S-LAAO or no S-LAAO. Intraoperative transesophageal echocardiogram (TEE) was recommended to assess successful closure using an endorsed technique. Oral anticoagulation was continued postoperatively. After a mean follow-up of 3.8 years, the primary endpoint of stroke or systemic embolism occurred in 4.8% of the S-LAAO group and 7.0% of the no S-LAAO group (HR, 0.67 [95% CI, 0.53-0.85];  $P=0.001$ ). Mortality rate, cross-clamp and bypass time, chest tube output, and bleeding were not different between groups. More than 75% of subjects in both groups received OAC. These data indicate S-LAAO provides additional benefit to oral anticoagulation without increasing risk of adverse events.

These findings cannot be extrapolated to patients without AF or patients who are not candidates for OAC. Most subjects underwent CABG or valve surgery, and the mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score was 4.2. Surgical AF ablation was performed in one-third of both groups. Patients undergoing mechanical valve surgery, transplant, off-pump bypass, left ventricular assistive device surgery, and congenital heart disease (CHD) cases were excluded. A subsequent meta-analysis of 5 RCTs and 22 observational studies including 540 111 patients showed a significant decrease in stroke and thromboembolism with S-LAAO.<sup>11</sup> The postoperative mortality rate did not differ but, in follow-up, was reduced in the S-LAAO group after 2 years. No difference in major bleeding, all-cause rehospitalizations, or cross-clamp time was observed.<sup>11</sup>

2. Substantial heterogeneity in S-LAAO methods exists in the literature, and not all techniques effectively exclude the LAA.<sup>4</sup> An increased risk of stroke and thromboembolism is associated with incomplete S-LAAO<sup>5,12</sup>; however, many studies do not report assessment of occlusion success.<sup>9</sup> This inconsistency has likely contributed to the variability in outcome.<sup>79</sup> LAAOS III permitted 4 techniques: amputation and closure (which was promoted as the preferred technique), used in 56%; stapler closure, used in 11%; double-layer linear closure (if confirmed by TEE), used in 14%; or an approved LAAO device, used in 15%. Other techniques were approved on a case-by-case basis (4%). Intraoperative TEE was recommended to assess successful closure, defined

as absence of flow across the suture line and a stump of  $<1$  cm. If the initial closure was unsuccessful, additional suturing was performed for repair. Contemporary data show closure success of  $>95\%$  using a surgical clip device.<sup>13</sup> In the LAAOS series, the mean cross-clamp and bypass times were similar, and perioperative bleeding was not increased in the S-LAAO group.<sup>14</sup> These data support the importance of complete S-LAAO in achieving beneficial outcomes.

3. In LAAOS III, S-LAAO reduced stroke and thromboembolism by 33% in addition to OAC. LAAOS III was not designed to resolve whether oral anticoagulation can be safely stopped after S-LAAO; at hospital discharge,  $>80\%$  of subjects in both groups were receiving OAC, with  $>75\%$  on OAC at the 3-year visit.<sup>1</sup> A systematic review and meta-analysis focusing on the effects of anticoagulation found no statistically significant difference in stroke rates of S-LAAO/no S-LAAO subjects on OAC versus off OAC, with high heterogeneity noted for both ischemic events and mortality,<sup>14</sup> and findings are subject to confounding by indication and the potentially beneficial effects of surgical AF ablation. The LAACS (Left Atrial Appendage Closure with Surgery) study of 187 subjects undergoing CABG, valve surgery, or both who were randomized to S-LAAO versus no S-LAAO showed a reduction in the risk of stroke in the S-LAAO group, independent of anticoagulation status.<sup>15</sup> These results must be interpreted with caution, however, because the study was not powered to demonstrate a reduction in stroke, and substantial crossover occurred.

## 6.6. Active Bleeding on Anticoagulant Therapy and Reversal Drugs

### Recommendations for Active Bleeding on Anticoagulant Therapy and Reversal Drugs

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

COR	LOE	Recommendations
1	B-NR	1. In patients with AF receiving dabigatran who develop life-threatening bleeding, treatment with idarucizumab is recommended to rapidly reverse dabigatran's anticoagulation effect. <sup>1-3</sup>
2a	C-LD	2. In patients with AF receiving dabigatran who develop life-threatening bleeding, treatment with activated prothrombin complex concentrate (PCC) is reasonable to reverse dabigatran's anticoagulation effect if idarucizumab is unavailable. <sup>4,5</sup>
1	B-NR*	3. In patients with AF receiving factor Xa inhibitors who develop life-threatening bleeding, treatment with either andexanet alfa (apixaban or rivaroxaban,* edoxaban†) or 4-factor prothrombin complex concentrate† is recommended to rapidly reverse factor Xa inhibitor's anticoagulation effect. <sup>6,7</sup>
	C-LD†	

Recommendations for Active Bleeding on Anticoagulant Therapy and Reversal Drugs (Continued)		
COR	LOE	Recommendations
1	A	4. In patients with AF receiving warfarin who develop life-threatening bleeding, treatment with 4-factor prothrombin complex concentrate (if available) in addition to intravenous vitamin K is recommended to rapidly achieve INR correction over fresh frozen plasma and intravenous vitamin K treatment. <sup>8-10</sup>
2b	B-NR	5. In patients with AF who develop major gastrointestinal bleeding, resumption of oral anticoagulation therapy may be reasonable after correction of reversible causes of bleeding and reassessment of its long-term benefits and risks with a multidisciplinary team approach during SDM with patients. <sup>11,12</sup>

\*B-NR LOE applies to data on apixaban or rivaroxaban. †C-LD LOE applies to data on edoxaban.

### Synopsis

About 2% to 4% of patients who receive OACs experience major bleeding and require intervention.<sup>13</sup> Activated charcoal may be administered up to 6 to 8 hours after the last dose of an OAC.<sup>14,15</sup> Hemodialysis may be also considered to eliminate dabigatran but may be challenging and impractical due to coagulopathy and hemodynamic instability.<sup>16</sup> The proportion of emergency department visits for bleeding from OACs due to DOACs increased from 2.3% in 2011 to 37.9% in 2017 because of the increased use of DOACs over the past decade.<sup>17</sup> Some patients may require reversal agents to achieve rapid hemostasis. Failure to achieve effective hemostasis is associated with a >3 times higher risk of death.<sup>18</sup> Idarucizumab for dabigatran-induced major bleeding and andexanet alfa for apixaban or rivaroxaban associated major bleeding are US Food and Drug Administration (FDA) approved. Four-factor PCC for DOAC-induced major bleeding was compared with andexanet alfa in retrospective cohort studies, but the comparison has never been investigated in clinical trials.<sup>7</sup> For VKA, if life-threatening bleeding cannot be managed with supportive measures, the rapid reversal treatment with 4-factor PCC is preferred over fresh frozen plasma.<sup>8-10</sup> Table 15 summarizes reversal agents for OACs. Table 16 describes bleeding events attributable to DOACs in pivotal clinical trials.

### Recommendation-Supportive Text

1. The RE-VERSE AD (Reversal of Dabigatran Anticoagulant Effect With Idarucizumab) study was a multicenter, prospective cohort study evaluating the use of idarucizumab in patients receiving dabigatran for the management of uncontrolled or life-threatening bleeding or in patients requiring urgent surgery or invasive procedure.<sup>1</sup> In patients with uncontrolled or life-threatening bleeding, idarucizumab reversed the dabigatran anticoagulation effect in 100% of patients, and 67.7% had bleeding cessation. Thrombosis events after the reversal agent use was 4.7% within 30 days. However, this

study did not have a control group. The post hoc analysis of the RE-VERSE AD study in patients with gastrointestinal bleeding found that 97.5% of patients achieved complete reversal of dabigatran, and bleeding cessation occurred in 76.2% of patients.<sup>2</sup> Another post hoc analysis of the same study showed that idarucizumab was effective at reversing dabigatran's anticoagulation effect, regardless of baseline renal function.<sup>3</sup>

2. Compared with idarucizumab, the data on PCC for dabigatran-associated bleeding are very limited. A prospective multicenter cohort study compared the use of activated PCC in 14 patients with dabigatran-associated major bleeding compared with historical matched cases.<sup>4</sup> The study was prematurely stopped due to the availability of idarucizumab in the market. The effectiveness of activated PCC was assessed based on the assessment guide rating from good, moderate, and poor. Nine patients (64%) were rated as good, 5 patients (36%) as moderate, and none as poor. No thromboembolic events were found. A randomized, placebo-controlled crossover trial in 12 healthy subjects evaluated the reversal effect of 4-factor PCC on rivaroxaban or dabigatran's effect.<sup>5</sup> It showed 4-factor PCC completely reversed rivaroxaban's effect based the prothrombin time, but it did not reverse dabigatran's effect based on the coagulation tests (aPTT, ecarin clotting time, and thrombin time). Four-factor PCC may not be appropriate for dabigatran-associated major bleeding management until further investigation is performed in prospective studies.
3. The ANNEXA 4 (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors) trial evaluated the use of andexanet alfa in adult patients with acute major bleeding (safety population, n=254; efficacy population, n=254) receiving factor Xa inhibitors (apixaban 55%, rivaroxaban 36%, edoxaban 3%, and enoxaparin 6%).<sup>6</sup> It found that after the bolus administration, the median anti-factor Xa activity decreased by 89%. Twelve hours after the andexanet infusion, clinical hemostasis was adjudicated as excellent or good in 37 of 47 patients in the efficacy analysis (79% [95% CI, 64%-89%]); however, thrombotic events occurred in 12 of 67 patients (18%) during the 30-day follow-up. Currently, andexanet alfa is FDA-approved for only apixaban- or rivaroxaban-associated life-threatening or uncontrolled bleeding, because only limited data are available for other factor Xa inhibitors. For 4-factor PCC, a meta-analysis of 22 observational studies compared andexanet alfa (n=438) with PCC (n=1278) in patients with acute bleeding associated with oral factor Xa

**Table 15. Reversal Agents for Oral Anticoagulants**

	Idarucizumab	Andexanet alfa	4-Factor PCC	Activated PCC
<b>Class</b>	Humanized monoclonal antibody fragment binding to dabigatran and neutralizing anticoagulation effects	A recombinant modified human factor Xa protein binding and sequestering the factor Xa inhibitors	PCC: coagulation factors II, VII, IX, and X Anticoagulation proteins C and S	Nonactivated factors II, IX, and X Activated VII
<b>FDA indications</b>	Reversal of dabigatran effects For emergency surgery/urgent procedures Life-threatening or uncontrolled bleeding	Reversal of apixaban or rivaroxaban For life-threatening or uncontrolled bleeding	The urgent reversal for acute major bleeding or need for an urgent surgery/invasive procedure in patients receiving VKAs	Control and prevention of bleeding episodes, perioperative management, prophylaxis to prevent or reduce bleeding frequency in patients with hemophilia A and B
<b>Off-label indications</b>	N/A	Edoxaban-associated life-threatening bleeding	Reversal of factor Xa inhibitors in patients requiring urgent procedure or with life-threatening bleeding	Dabigatran-associated life-threatening bleeding
<b>Dosing</b>	5-g (2 separate vials of 2.5 g/vial) intravenous infusion over 5 min. Additional 5 g may be given if reappearance of bleeding with elevated coagulation parameters have been observed or patients require second emergency surgery/procedure and elevated coagulation parameters	Low-dose regimen: 400-mg bolus at a target rate of 30 mg/min followed by 4 mg/min for up to 120 min High-dose regimen: 800-mg bolus at a target rate of 30 mg/min followed by 8 mg/min for up to 120 min The recommended dosing is based on apixaban or rivaroxaban, dose, and time since the patient's last dose of apixaban or rivaroxaban	Warfarin reversal based on pretreatment INR (units of factor IX): 1. INR 2–<4: 25 units/kg (up to 2500 units) 2. INR 4–6: 35 units/kg (up to 3500 units) 3. INR >6: 50 units/kg (up to 5000 units) Oral factor Xa inhibitors: 2000 units once or 25 to 50 units/kg	Dabigatran-associated life-threatening bleeding: 50 units/kg once
<b>Onset</b>	Within 5 min	Within 2 min	Within 10 min	Within 30 min
<b>Duration</b>	12-24 h	2 h	8 h	12 h
<b>Monitoring</b>	Coagulation parameters (aPTT, diluted thrombin time, or ecarin clotting time) between 12 and 24 h to assess redistribution of dabigatran from peripheral to plasma	Current commercial anti-Xa activity assays are unsuitable for measuring factor Xa activities after andexanet alfa use	Warfarin reversal: Repeat INR within 30 min after the administration	N/A
<b>Others</b>	Risk of serious reactions (hypoglycemia, hypophosphatemia, metabolic acidosis, increase in uric acid, acute liver failure) in patients with hereditary fructose intolerance (due to sorbitol excipient 4 g in each 5 g of idarucizumab) No procoagulant effect based on endogenous thrombin potential	No FDA indication for other factor Xa inhibitors other than apixaban or rivaroxaban Andexanet alfa may interfere with the anticoagulation effect of heparin US black box warning: Serious and life-threatening adverse events (arterial and venous thromboembolism, myocardial infarction, ischemic stroke, cardiac arrest, sudden deaths)	May not be indicated for patients with thromboembolic events in the previous 3 mo It includes heparin Administer intravenous vitamin K 10 mg over 10-20 min in addition to 4-factor PCC	It does not include heparin Coagulation parameters do not correlate with the drug's efficacy Not effective to reverse factor Xa inhibitors

Information in table was obtained from manufacturer package inserts.

aPTT indicates activated partial thromboplastin time; FDA, US Food and Drug Administration; PCC, prothrombin complex concentrate; and VKA, vitamin K antagonists.

inhibitors.<sup>7</sup> It showed that mean hemostatic effectiveness for andexanet alfa was 82% at 12 hours and 71% at 24 hours versus 88% at 12 hours and 76% at 24 hours for PCC. Mean 30-day venous thromboembolism rate was 5.0% in the andexanet alfa group versus 1.9% in the PCC group. However, the meta-analysis had more significant methodological issues than the ANNEXA 4 trial. Thus, the level of evidence for the 4-factor PCC use was downgraded.

4. A meta-analysis of 13 studies (5 randomized trials and 8 observational studies) compared 4-factor PCC with fresh frozen plasma for warfarin-associated bleeding or urgent surgery/procedure.<sup>8</sup> Four-factor PCC use was significantly associated with lower risk of all-cause mortality (25.1% versus 28.8%; OR, 0.56 [95% CI, 0.37-0.84]), higher probability to achieve INR correction (60.6% versus 12.8%; OR, 10.8 [95% CI, 6.12-19.07]), shortened time to INR correction (−6.5 h [95% CI, −9.75 h to −3.24 h]),

**Table 16. Bleeding Events (Percentage Per Year) in DOAC Pivotal Clinical Trials**

Bleeding Event	RE-LY (n=18 113)	ARISTOTLE (n=18 201)	ENGAGE AF-TIMI 48 (n=21 105)	ROCKET AF (n=14 264)
Major bleeding	Dabigatran 150 mg 3.11% (RR, 0.93 [95% CI, 0.81–1.07]; P=0.31) Dabigatran 110 mg 2.71% (RR, 0.80 [95% CI, 0.69–0.93]; P=0.003) Warfarin 3.36%	Apixaban 2.13% (HR, 0.69 [95% CI, 0.60–0.80]; P<0.001) Warfarin 3.09%	Edoxaban 60 mg 2.75% vs warfarin 3.43% (HR, 0.80 [95% CI, 0.71–0.91]; P<0.001) Edoxaban 30 mg 1.61% vs warfarin 3.43% (HR, 0.47 [95% CI, 0.41–0.55]; P<0.001)	Rivaroxaban 3.6% vs warfarin 3.4% (HR, 1.04 [95% CI, 0.90–1.20]; P=0.58)
Gastrointestinal bleeding	Dabigatran 150 mg 1.51% vs warfarin 1.02% (RR, 1.50 [95% CI, 1.19–1.89]; P<0.001) Dabigatran 110 mg 1.12% vs warfarin 1.02% (RR, 1.10 [95% CI, 0.86–1.41]; P=0.43)	Apixaban 0.76% (HR, 0.89 [95% CI, 0.70–1.15]; P=0.37) Warfarin 0.86%	Edoxaban 60 mg 1.51% (HR, 1.23 [95% CI, 1.02–1.50]; P=0.03) Edoxaban 30 mg 0.82% (HR, 0.67 [95% CI, 0.53–0.83]; P<0.001) Warfarin 1.23%	Rivaroxaban 3.2% (HR not reported; P<0.001) Warfarin 2.2%
Intracranial bleeding	Dabigatran 150 mg 0.30% (RR, 0.40 [95% CI, 0.27–0.60]; P<0.001) Dabigatran 110 mg 0.23% (RR, 0.31 [95% CI, 0.20–0.47]; P<0.001) Warfarin 0.74%	Apixaban 0.33% (HR, 0.42 [95% CI, 0.30–0.58]; P<0.001) Warfarin 0.80%	Edoxaban 60 mg 0.39% (HR, 0.47 [95% CI, 0.34–0.63]; P<0.001) Edoxaban 30 mg 0.26% (HR, 0.30 [95% CI, 0.21–0.43]; P<0.001) Warfarin 0.85%	Rivaroxaban 0.80% (HR, 0.67 [95% CI, 0.47–0.93]; P=0.02) Warfarin 1.20%

Adapted with permission from Kido et al.<sup>22</sup> Copyright 2021 American College of Clinical Pharmacy.

ARISTOTLE indicates Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; DOAC, direct anticoagulant; ENGAGE AF-TIMI 48, Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation – Thrombolysis in Myocardial Infarction 48; HR indicates hazard ratio; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; and RR, relative risk.

and lower risk of volume overload (2.1% versus 8.8%; OR, 0.27 [95% CI, 0.13-0.58]) compared with fresh frozen plasma. No significant difference in thromboembolic events (4.2% versus 4.8%; OR, 0.91 [95% CI, 0.44-1.89]; P=0.81) was found.

- A meta-analysis of 10 cohort studies compared anticoagulation resumption (n=2080) versus discontinuation (n=2296) after gastrointestinal bleeding in patients receiving OACs for AF, venous thromboembolism, or prosthetic valve.<sup>11</sup> Restarting anticoagulation was significantly associated with higher risks of recurrent gastrointestinal bleeding (10.1% versus 5.3%) but also with lower risks of thromboembolic events (6.3% versus 10.6%) and a reduction in all-cause mortality (21.3% versus 31%). Another meta-analysis of 7 observational studies in patients with AF found no significant difference in stroke rates between resumption and discontinuation groups (9.1% versus 8.3%; OR, 0.75 [95% CI, 0.37-1.51]).<sup>12</sup> Resumption of anticoagulation therapy was associated with significant reduction in any thromboembolic events (8.0% versus 12.2%; OR, 0.54 [95% CI, 0.43-0.68]) and all-cause mortality (10.8% absolute risk reduction; OR, 0.38 [95% CI, 0.24-0.60]), at the expense of recurrent major bleeding (10.2% versus 5.0%). One study found the optimal timing of resuming a VKA after upper

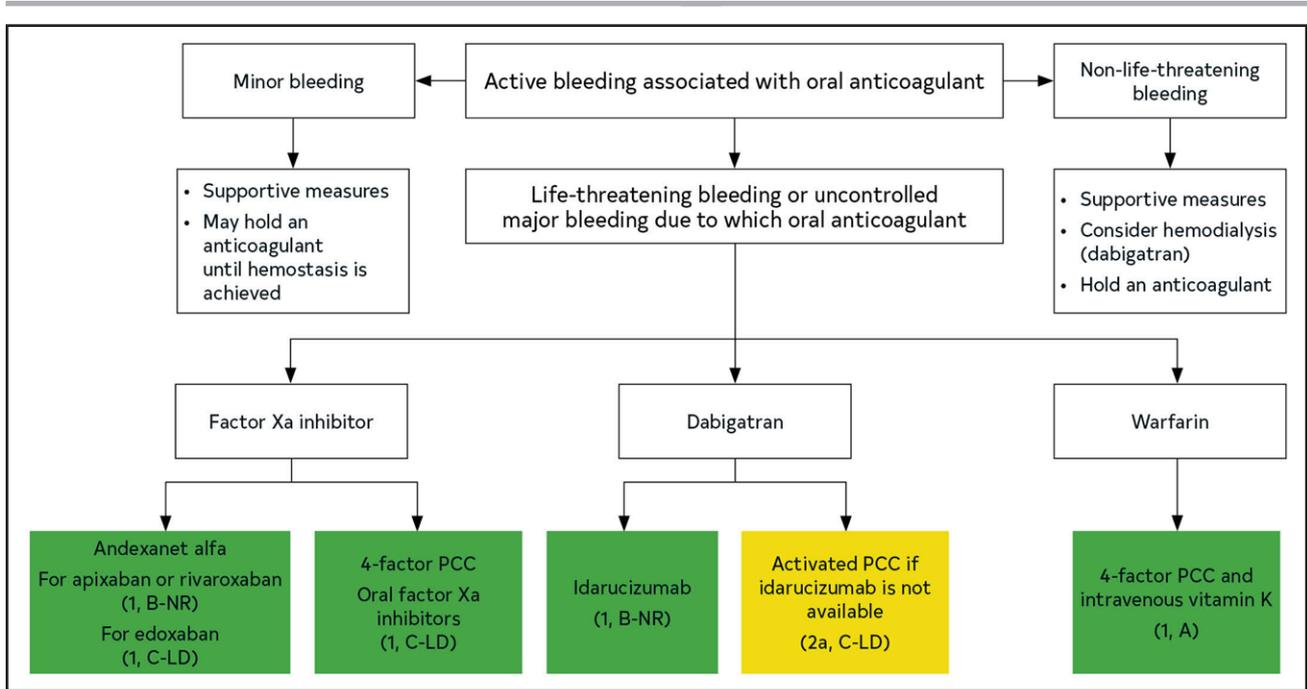
gastrointestinal bleeding was between 3 and 6 weeks, while other studies revealed that resuming a VKA 1 week after gastrointestinal bleeding is the optimal timing.<sup>19–21</sup> There is a paucity of data evaluating the timing of DOACs after gastrointestinal bleeding.

**6.6.1. Management of Patients With AF and ICH**

Recommendations for Management of Patients With AF and ICH		
Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
2a	C-LD	1. In patients with AF and conditions associated with very high risk of thromboembolic events (>5%/year), such as rheumatic heart disease or a mechanical heart valve, early (1-2 weeks) resumption of anticoagulation after ICH is reasonable to reduce the risk of thromboembolic events. <sup>1</sup>
2b	C-LD	2. In patients with AF and ICH, delayed (4-8 weeks) resumption of anticoagulation may be considered to balance the risks of thromboembolic and hemorrhagic complications after careful risk benefit assessment. <sup>2–5</sup>
2b	B-NR	3. In patients with AF and conditions associated with high risk of recurrent ICH (eg, cerebral amyloid angiopathy) anticoagulation-sparing strategies (eg, LAAO) may be considered to reduce the risk of recurrent hemorrhage. <sup>6,7</sup>

**Synopsis**

ICH is a term that refers to bleeding within any of the compartments of the cranial vault, including intraparenchymal



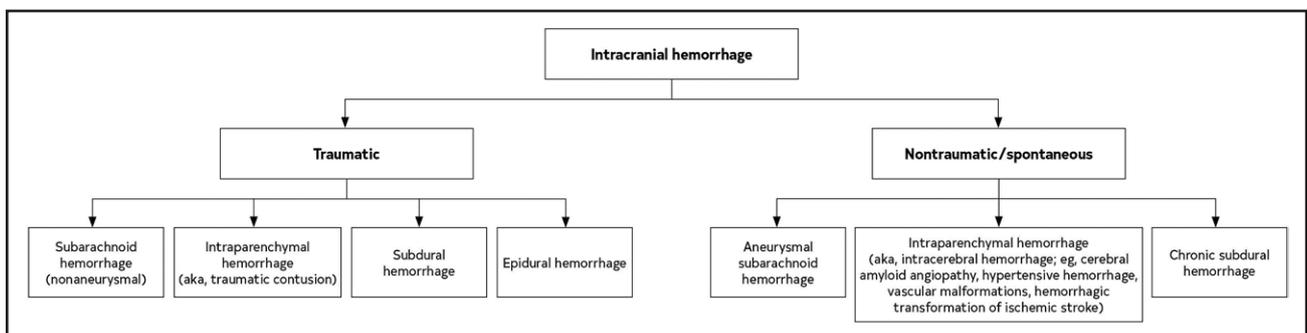
**Figure 13. Active Bleeding Associated With Oral Anticoagulant.** Colors correspond to Table 2. PCC indicates prothrombin complex concentrate.

(or intracerebral), subarachnoid, subdural, and epidural hemorrhage. In clinical practice, the different forms of ICH are often classified by mechanism and most broadly as traumatic and nontraumatic or spontaneous ICHs (Figure 14). In patients with AF and conditions associated with high-risk for thromboembolic complications (eg, mechanical valve, rheumatic valvular disease), anticoagulation is often resumed early after ICH, regardless of mechanism. For other patients with AF, decisions regarding if (and when) to resume anticoagulation after ICH requires more careful risk-benefit assessment of patient-specific clinical factors. Patients with traumatic etiologies generally have lower long-term risk of recurrent hemorrhage, and anticoagulation is generally considered safe to resume. Nontraumatic/spontaneous etiologies (eg, hypertensive parenchymal hemorrhage, hemorrhagic transformation after isch-

emic stroke, cerebral amyloid angiopathy-associated hemorrhage, chronic subdural hemorrhage) are generally associated with higher risk of recurrence. Clinical decision-making regarding the appropriateness of resumption in these patients is based largely on individual risk-benefit calculations given the lack of randomized data assessing safety and long-term outcomes. For patients with ICH deemed at high risk of recurrence, LAA closure may be a viable alternative to anticoagulation, although data on efficacy and safety are lacking in the ICH population.

**Recommendation-Specific Supportive Text**

1. Rheumatic valvular disease is associated with a >5% per year risk of embolic events.<sup>8</sup> In patients with mechanical heart valves, the rate can range from 4% to 23% per year depending on the type



**Figure 14. Forms of ICH, Classified by Mechanism.** ICH indicates intracranial hemorrhage.

and position of the prosthetic.<sup>9-11</sup> These rates are even higher in patients with concurrent AF but are significantly reduced with the use of VKAs. Data are limited that explore the safety and timing of anticoagulation resumption in patients with ICH and high-risk valvular disease. In 1 observational analysis of 137 patients with ICH and mechanical heart valves, resuming anticoagulation within 2 weeks from index ICH was associated with increased hemorrhagic complications (HR, 7.06 [95% CI, 2.33-21.37]).<sup>1</sup> However, in balancing the risk of hemorrhagic with thrombotic complications, the optimal window of resumption was found to be between 1 and 2 weeks post-ICH after weighing individual patient factors (Table 17).

2. Anticoagulation is associated with up to 25% of ICHs and is associated with worse functional outcomes and higher mortality.<sup>12-15</sup> After ICH, anticoagulation is generally held in the acute setting. Decisions regarding the appropriateness and timing of resumption are complex given the limited amount of randomized data addressing risks and benefits in this population. Previous observational reports evaluating risk of recurrent ICH, thromboembolism, and mortality in patients with nonvalvular AF have suggested possible reduction in thromboembolic risk and mortality with resumption of anticoagulation but are limited by discordant patient populations and study designs, predominant use of VKAs, and potential selection

biases.<sup>16-22</sup> In a meta-analysis of 2452 patients with AF and ICH, resumption of OACs was associated with lower risk of ischemic stroke (RR, 0.46 [95% CI, 0.29-0.72]) and no difference in risk of recurrent ICH compared with patients in whom anticoagulation was not resumed<sup>2</sup> (Table 17). However, data are limited on the optimal timing for resumption. In an analysis of 2619 ICH survivors with AF, a composite net benefit minimizing risk of bleeding and thromboembolic complications occurred when anticoagulation was resumed at 7 to 8 weeks after ICH.<sup>3</sup> In a retrospective study that included 1752 patients with OAC-related ICH across 3 Danish registries, anticoagulation resumed a median of 34 days was associated with an adjusted HR of ischemic stroke, systemic embolism, and all-cause mortality of 0.55 (95% CI, 0.39-0.78) compared with no anticoagulation.<sup>4</sup> In another meta-analysis of 8 observational studies, resuming OAC was associated with reduced risk of ischemic stroke without increased risk of recurrent ICH at a median time to resumption of 10 to 39 days<sup>5</sup> (Table 17). Of note, DOACs have been associated with lower rates of major bleeding complications compared with VKAs.<sup>23</sup>

3. Anticoagulation is used for stroke risk reduction in patients with AF at risk of thromboembolism. For some patients, however, risk of recurrent ICH may be prohibitively high with anticoagulation. Cerebral amyloid angiopathy is the most common cause of lobar hemorrhage in older adults and is associated with annual ICH recurrence risk that ranges from 5% in patients with isolated microhemorrhages to 26.9% in patients with associated cortical superficial siderosis.<sup>24</sup> Thus, in patients with AF and cerebral amyloid angiopathy-related ICH, alternative strategies for secondary stroke prevention are often pursued. The LAA is considered the most common site for thrombus formation in patients with AF.<sup>25,26</sup> Two RCTs—PROTECT AF study and PREVAIL study—compared rates of stroke and mortality after LAA closure versus VKA in patients with AF.<sup>6,7</sup> In a meta-analysis examining 5-year outcomes in the 2 RCTs, LAA closure was associated with significant reductions in hemorrhagic stroke, disabling and fatal stroke, and all-cause mortality, with comparable rates of stroke and systemic embolism compared with warfarin.<sup>27</sup> Of note, both studies excluded patients who were not candidates for anticoagulation. Additionally, newer treatment options such as epicardial LAA clipping are emerging for stroke prevention without need for postprocedure APT.<sup>28,29</sup>

**Table 17. Risk Factors for Thromboembolic Complications and Recurrent ICH**

Factors Associated With High Risk of Thromboembolism	Factors Associated With High Risk of Recurrent ICH
Mechanical heart valve	Suspected cerebral amyloid angiopathy
Rheumatic valve disease	Lobar IPH
Previous history of stroke/thromboembolism	Older age
Hypercoagulable state (eg, active malignancy, genetic thrombophilia)	>10 cerebral microbleeds on MRI
High CHA <sub>2</sub> DS <sub>2</sub> -VASc score (>5)	Disseminated cortical superficial siderosis on MRI
	Poorly controlled hypertension
	Previous history of spontaneous ICH
	Genetic/acquired coagulopathy
	Untreated symptomatic vascular malformation or aneurysm

CHA<sub>2</sub>DS<sub>2</sub>-VASc indicates congestive heart failure, hypertension, age ≥75 y (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 y, sex category; ICH, intracranial hemorrhage; IPH, intraparenchymal hemorrhage; and MRI, magnetic resonance imaging.

### 6.7. Perioperative Management

Recommendations for Perioperative Management Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	B-R*	1. In patients with AF (excluding those with recent stroke or TIA, or a mechanical valve) and on oral anticoagulation with either warfarin* or DOAC† who are scheduled to undergo an invasive procedure or surgery, temporary cessation of oral anticoagulation without bridging anticoagulation is recommended. <sup>1-4</sup>
	B-NR†	
1	A	2. In patients with AF on warfarin anticoagulation and an annual predicted risk of thromboembolism of ≥5% undergoing pacemaker or defibrillator implantation or generator change, continued anticoagulation is recommended in preference to interruption of warfarin and bridging anticoagulation with heparin to reduce the risk of pocket hematoma. <sup>5-7</sup>
2a	A	3. In patients with AF with CHA <sub>2</sub> DS <sub>2</sub> -VASc score ≥2 or equivalent risk of stroke, on DOAC anticoagulation and undergoing pacemaker or defibrillator implantation or generator change, either uninterrupted or interrupted DOAC is reasonable. <sup>8-10</sup>
1	B-NR	4. In patients with AF on DOAC and scheduled to undergo an invasive procedure or surgery that cannot be performed safely on uninterrupted anticoagulation, the timing of interruption of DOAC should be guided by the specific agent, renal function, and the bleeding risk of the procedure (Table 18). <sup>4,11,12</sup>
2a	B-NR	5. In patients with AF on DOAC that has been interrupted for an invasive procedure or surgery, in general, resumption of anticoagulation the day after low bleeding risk surgery and between the evening of the second day and the evening of the third day after high bleeding risk surgery is reasonable, as long as hemostasis has been achieved and further bleeding is not anticipated. <sup>4</sup>
3: Harm	B-R	6. In patients with AF on warfarin anticoagulation, who are undergoing surgeries or procedures for which they are holding warfarin, except in patients with mechanical valve or recent stroke or TIA, bridging anticoagulation with low-molecular-weight heparin should not be administered. <sup>1,3,13-15</sup>

\*B-R LOE applies to the data on warfarin. †B-NR LOE applies to the data on DOAC.

#### Synopsis

Perioperative anticoagulation management is driven by 2 competing aims: to hold the anticoagulant agent for the shortest possible time to minimize the risk of thromboembolism and to ensure coagulation parameters are as close to normal as possible at the time of the procedure to facilitate hemostasis and avoid intra- and postoperative bleeding. Considerations include the bleeding risk of the procedure, consequences of bleeding should it occur, patient-specific risk factors, and thrombotic risk while off anticoagulation. Invasive procedures and surgeries have been divided into high and low bleeding risks in several different classifications.<sup>16</sup> Generally, endoscopic, dental extraction, many ophthalmologic procedures, and percutaneous vascular access, such as cardiac catheterization, are considered to be of low bleeding risk. Higher bleeding risk surgeries include intra-abdominal, pelvic, orthopedic,

neurosurgical, cardiac, and transvenous lead extraction procedures. Very high bleeding risk procedures include neuraxial anesthesia and spinal surgery. Available data do not suggest high rates of bleeding from these procedures, although bleeding could cause significant consequences.<sup>17</sup> Patient-specific factors include abnormal liver and kidney function, bleeding or clotting disorders, concomitant antiplatelet or nonsteroidal anti-inflammatory use, alcohol, and anemia. Recent bleeding or thromboembolism may increase the risk for recurrent events. To put thrombotic risk in perspective, the incidence of thromboembolism while anticoagulation was temporarily held has generally been <1%.<sup>3,18</sup>

#### Recommendation-Specific Supportive Text

1. To mitigate thromboembolic risk during interruption of warfarin therapy for a procedure or surgery, “bridging” anticoagulation can be administered. However, observational studies consistently showed an increased risk of bleeding without a difference in thromboembolic risk with this strategy.<sup>3</sup> The BRIDGE (Bridging Anticoagulation in Patients who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery) trial included patients with a mean CHADS<sub>2</sub> score of 2.3 (range, 1-6); 61.7% of patients had a CHADS<sub>2</sub> score <3.<sup>1</sup> In this study, discussed in more depth below, interruption of warfarin without bridging anticoagulation was superior to bridging.<sup>1</sup> In a meta-analysis of 6 observational studies reporting on patients not at high thromboembolic risk receiving prophylactic dose or no bridging had an overall thromboembolic event

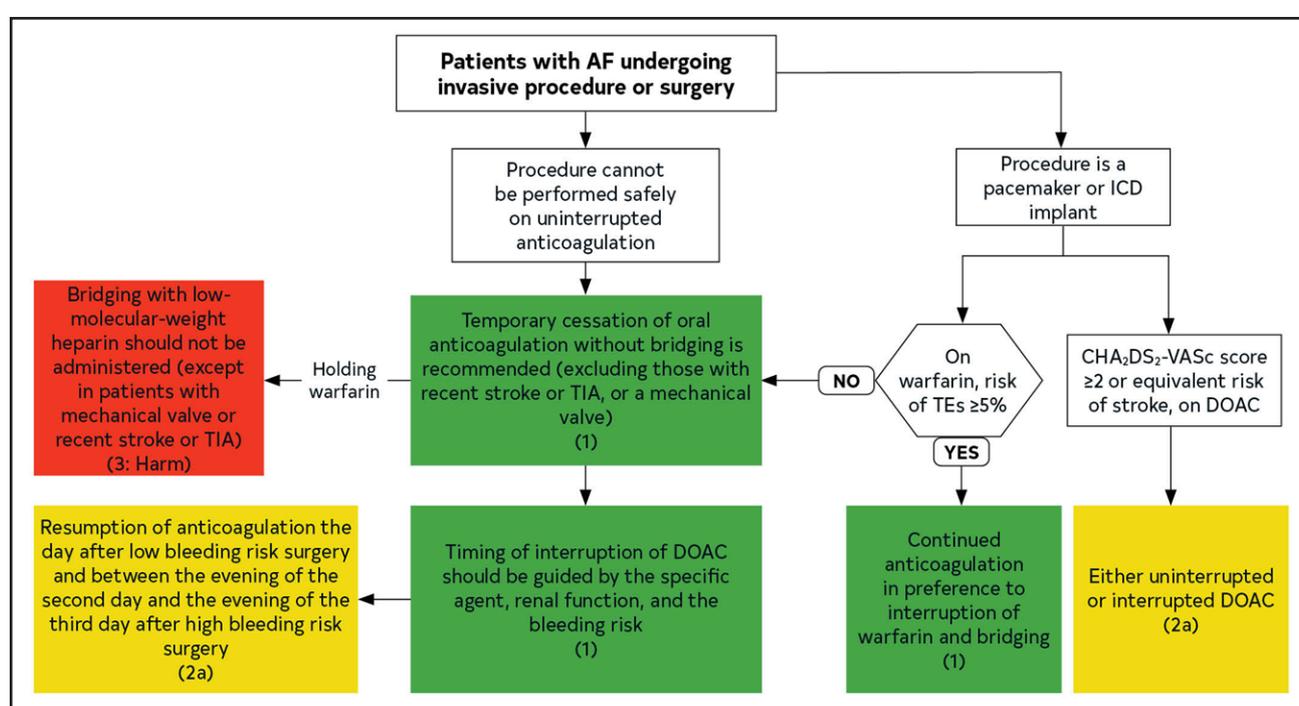
**Table 18. Timing of Discontinuation of OACs in Patients With AF Scheduled to Undergo an Invasive Procedure or Surgery in Whom Anticoagulation Is to Be Interrupted**

Anticoagulant	Low Bleeding Risk Procedure	High Bleeding Risk Procedure
Apixaban (CrCl >25 mL/min)*	1 d†	2 d
Dabigatran (CrCl >50 mL/min)	1 d	2 d
Dabigatran (CrCl 30-50 mL/min)	2 d	4 d
Edoxaban (CrCl >15 mL/min)	1 d	2 d
Rivaroxaban (CrCl >30 mL/min)	1 d	2 d
Warfarin	5 d for a target INR <1.5 2-3 d for a target INR <2	5 d

\*For patients on DOAC with creatinine clearance lower than the values in the table, few clinical data exist. Consider holding for an additional 1 to 3 days, especially for high bleeding risk procedures.

†The number of days is the number of full days before the day of surgery in which the patient does not take any dose of anticoagulant. The drug is also not taken the day of surgery. For example, in the case of holding a twice daily drug for 1 day, if the drug is taken at 8 pm, and surgery is at 8 am, at the time of surgery, it will be 36 hours since the last dose was taken.

AF indicates atrial fibrillation; CrCl, creatinine clearance; DOAC, direct oral anticoagulation; INR, international normalized ratio; and OAC, oral anticoagulant.



**Figure 15. Flowchart: Management of Perioperative Anticoagulation in Patients With AF.**

Colors correspond to Table 2. AF indicates atrial fibrillation; CHA<sub>2</sub>DS<sub>2</sub>-VASc, congestive heart failure, hypertension, age ≥75 y (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 y, sex category; DOAC, direct oral anticoagulant; ICD, implantable cardioverter-defibrillator; TE, thromboembolism; and TIA, transient ischemic attack.

rate of 0.6% (11 of 1702).<sup>3</sup> A similar RCT has not been done in the DOAC era, given the ease of brief interruption of DOAC therapy; however, observational studies have shown similar results.<sup>2</sup> The PAUSE (Perioperative Anticoagulation Use for Surgery Evaluation) cohort study, discussed below, enrolling patients with a mean CHADS<sub>2</sub> score of 2.1 (range, 1-6) and CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 3.5 (range, 1-9), found a low incidence of thromboembolic events when DOAC was briefly interrupted without bridging.<sup>4</sup> This suggests that in patients at low-to-moderate thromboembolic risk, interruption of anticoagulation, without bridging, may provide a low risk of bleeding with an acceptable risk of stroke/TIA. Patients with mechanical valves, and recent stroke/TIA, or other high-risk markers, were not included in most studies and may still benefit from bridging anticoagulation: in these scenarios, management should be individualized.

- Evidence has accrued that perioperative unfractionated or low-molecular-weight heparin bridging has been associated with an increased risk of pocket hematoma after pacemaker or ICD procedures.<sup>19</sup> BRUISE-CONTROL (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial) randomized patients with AF (88%) or a mechanical valve with an estimated annual stroke risk of ≥5%, and undergoing elective device surgery, to continued

warfarin versus warfarin interruption with bridging anticoagulation. The incidence of clinically significant pocket hematoma was >4 times higher in the bridging group.<sup>5</sup> Several other procedures have been performed on uninterrupted anticoagulation.<sup>20</sup> Further study is needed to define which procedures, in which patients, can safely be performed with uninterrupted anticoagulation. Lead extraction procedures are generally considered high bleeding risk and therefore should be treated as such (high bleeding risk procedures in Table 18) and warfarin interrupted, with occasional exceptions.

- Two RCTs and several observational studies have shown little or no difference in the risk of pocket hematoma and thromboembolic events in patients with AF anticoagulated with DOACs and undergoing device surgery.<sup>9-10</sup> Therefore, brief interruption of DOAC therapy (low bleeding risk procedures in Table 18) may be preferable for many, while uninterrupted DOAC may be preferred for those at particularly high thromboembolic risk. Lead extraction procedures are generally considered high bleeding risk and therefore should be treated as such (high bleeding risk procedures in Table 18) and DOAC interrupted, with occasional exceptions.
- To achieve the goals of reducing or eliminating anticoagulant effect at the time of surgery, while also minimizing the time the patient spends without

anticoagulation to prevent thromboembolism, the duration of cessation of anticoagulation should take into account both the pharmacokinetics and pharmacodynamics of the agent, the patient's renal function, and the bleeding risk of the procedure. Direct measurement of DOAC levels is unavailable in clinical practice, but levels <30 ng/mL, which correspond to the expected plasma DOAC concentration reached after 3 half-lives, when most of the drug (87.5% of the C<sub>max</sub>) has been eliminated, is reached in two-thirds of patients 24 to 48 hours after the last drug intake.<sup>11</sup> Similar results were observed for apixaban.<sup>12</sup> A drug "hold" of 48 hours in clinical practice typically means 2 full days without drug intake, in addition to the day of the procedure, leading to a longer interval between last drug intake and procedure start longer than 48 hours, usually an additional 12 hours. Meta-analysis of the reports of periprocedural events from the pivotal trials of each of the 4 available DOACs suggested similar outcomes in patients on DOAC or warfarin, with reduced major bleeding during an uninterrupted strategy with DOACs.<sup>21</sup> The PAUSE protocol was studied in patients on apixaban, dabigatran, and rivaroxaban, and resulted in low rates of major bleeding (0.9%-1.85%) and thromboembolism (<1%). A high rate (>90%) of minimal anticoagulant level (<50 ng/mL) was achieved. Similar results have been observed with edoxaban in clinical practice.<sup>22</sup> Different protocols have not been directly compared. Table 18 presents recommended DOAC interruption times based on agent, renal function, and the bleeding risk of the procedure.

5. The timing of resumption of interrupted anticoagulation after surgery is a complex decision that should integrate patient and surgical characteristics. Warfarin, which takes several days (usually 3-5) to become therapeutic, can often be restarted the evening of the procedure. Postoperative bridging anticoagulation has not been shown to be generally beneficial.<sup>1,13</sup> In the PAUSE study, DOACs were started on the first postoperative day for low bleeding risk procedures and between the evening of the second and third postoperative days for high bleeding risk procedures. This resulted in a low risk of major bleeding.<sup>4</sup> Input from the proceduralist should always be incorporated into decisions.
6. Several studies have compared a strategy of bridging anticoagulation with a comparator of no bridging in patients on anticoagulants who were scheduled to undergo an invasive procedure or surgery. The BRIDGE trial randomized 1 884 patients with AF or AFL to bridging anticoagulation before and after the procedure with dalteparin versus placebo.<sup>1</sup> Almost 90% of patients were undergoing

low bleeding risk procedures. No bridging was superior to bridging with respect to major bleeding and was noninferior with respect to thromboembolism, although the observed rate (0.4%) was lower than anticipated (1.0%). PERIOP2 (A Double Blind Randomized Control Trial of Post-Operative Low Molecular Weight Heparin Bridging Therapy Versus Placebo Bridging Therapy for Patients Who Are at High Risk for Arterial Thromboembolism) randomized patients, about two-thirds of whom were undergoing high bleeding risk procedures, and 79% of whom had AF, to postoperative bridging with dalteparin or placebo until the INR was >1.9. All patients received preoperative bridging. Bleeding and thromboembolism outcomes were similar.<sup>13</sup> These studies also excluded patients with recent bleeding or thromboembolism, and those undergoing spinal and neurological surgery, and in these cases, management should be individualized and may include bridging anticoagulation.<sup>1,13</sup> A small randomized trial found that dental extractions could be performed on uninterrupted warfarin without bridging.<sup>14</sup> A large multicenter registry also did not find a difference in thromboembolism, but an increase in bleeding, in bridged patients.<sup>15</sup> Patients with mechanical valves should be managed as outlined in the "2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease."<sup>23</sup>

## 6.8. Anticoagulation in Specific Populations

### 6.8.1. AF Complicating ACS or Percutaneous Coronary Intervention (PCI)

Recommendations for AF Complicating ACS or PCI		
Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	A	1. In patients with AF and an increased risk for stroke who undergo PCI, DOACs are preferred over VKAs in combination with APT to reduce the risk of clinically relevant bleeding. <sup>1-5</sup>
1	A	2. In most patients with AF who take oral anticoagulation and undergo PCI, early discontinuation of aspirin (1-4 wk) and continuation of dual antithrombotic therapy with OAC and a P2Y12 inhibitor is preferred over triple therapy (OAC, P2Y12 inhibitor, and aspirin) to reduce the risk of clinically relevant bleeding. <sup>1-4,6</sup>

#### Synopsis

Encountering a patient with AF at an increased risk for stroke who undergoes PCI for stable CAD or ACS is a common clinical scenario. The addition of APT to OAC after PCI introduces a risk for clinically significant bleeding. RCTs have compared the safety and efficacy of various antithrombotic regimens after PCI is performed in patients with AF. They have consistently shown that DOACs, when used in conjunction with APT, are associated

with a lower risk of clinically relevant bleeding compared to VKAs.<sup>1-5</sup> They have also shown that dual therapy with an OAC and single APT with a P2Y12 inhibitor significantly lowers the risk of clinically relevant bleeding compared with triple therapy (oral anticoagulation, P2Y12 inhibitor, and aspirin) without substantially increasing risk of major adverse cardiovascular events.<sup>1-4,6</sup> Meta-analyses of these trials have shown a slightly increased risk of stent thrombosis with dual therapy compared to triple therapy.<sup>5</sup> Thus, the risk of stent thrombosis must be weighed against the risk of bleeding in determining the antithrombotic regimen after PCI. This is particularly true in patients with a relatively high perceived risk of stent thrombosis (complex revascularization, multivessel PCI, previous history of stent thrombosis).

**Recommendation-Specific Supportive Text**

1. Post-PCI antithrombotic regimens comparing DOACs with VKAs in combination with APT in patients with AF who do not have a specific indication for VKAs (eg, mechanical valve) have consistently shown a reduction in clinically relevant bleeding.<sup>1,2,4</sup> A meta-analysis of 3 RCTs comparing DOACs with VKAs after PCI, 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) (rivaroxaban), RE-DUAL PCI trial (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) (dabigatran), and AUGUSTUS (Open-Label, 2x2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban vs Vitamin K Antagonist and Aspirin vs Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome and/or Percutaneous Coronary Intervention) (apixaban), showed a 42% relative risk reduction for major bleeding in DOAC-based regimens compared with VKA-based regimens (OR, 0.577 [95% CI, 0.477-0.698];  $P<0.001$ ).<sup>5</sup> There was no statistically significant difference in the risk of ischemic events between groups. The ENTRUST-AF PCI (Edoxaban Treatment vs Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial showed that edoxaban-based regimens were noninferior to VKA-based regimens in terms of clinically relevant bleeding after PCI.<sup>3</sup> An important limitation of the aforementioned data is that most studies compared DOACs monotherapy against VKA plus aspirin, the only VKA-based dual antithrombotic therapy

(DAT) regimen was available in AUGUSTUS trial, thus providing limited information in comparison to DOAC-based DAT regimens available in all trials.<sup>5</sup>

2. RCTs have supported DAT with OAC and a P2Y12 inhibitor over triple therapy with OAC, P2Y12 inhibitor, and aspirin to reduce the risk of clinically relevant bleeding in patients with AF after PCI, including WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) (VKA), PIONEER AF-PCI (rivaroxaban), RE-DUAL (dabigatran), and AUGUSTUS (apixaban).<sup>1,2,4,6</sup> A meta-analysis of PIONEER AF-PCI, RE-DUAL, and AUGUSTUS demonstrated a 40% relative risk reduction for International Society on Thrombosis and Haemostasis major bleeding in dual therapy regimens compared with triple therapy (OR, 0.598 [95% CI, 0.491-0.727];  $P<0.001$ ).<sup>5</sup> Patients in the intervention group received varying duration of triple therapy with aspirin after PCI up to 7 days. This meta-analysis showed that DAT with DOAC and P2Y12 inhibitor was associated with an increased risk of stent thrombosis (OR, 1.672 [95% CI, 1.022-2.733];  $P=0.041$ ) compared with triple therapy.<sup>5</sup> This finding was mainly driven by outcomes in the 110-mg dosing group of dabigatran in the RE-DUAL trial. The number needed to treat for International Society on Thrombosis and Haemostasis major bleeding (n=42) was substantially lower than the number needed to harm for stent thrombosis (n=223) with DAT compared with triple therapy.<sup>5</sup> Based on these findings, extended triple therapy up to 30 days after PCI is a consideration when the perceived risk of stent thrombosis is high (eg, complex revascularization, multivessel PCI, previous history of stent thrombosis).

**6.8.2. Chronic Coronary Disease (CCD)**

Recommendation for CCD		
Referenced studies that support the recommendation are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendation
1	B-R	1. In patients with AF and CCD (beyond 1 year after revascularization or CAD not requiring coronary revascularization) without history of stent thrombosis, oral anticoagulation monotherapy is recommended over the combination therapy of OAC and single APT (aspirin or P2Y12 inhibitor) to decrease the risk of major bleeding. <sup>1-3</sup>

**Synopsis**

APT is the first-line therapy to prevent recurrent cardiovascular events in patients with CAD, while anticoagulation therapy is recommended to prevent stroke or systemic embolism in patients with AF at increased risk of thromboembolism. Minimal evidence was available until recently if a combination therapy of APT in addition to OAC therapy provides additional value to prevent cardiovascular

events in patients with AF and concomitant CCD (at least 12 months after revascularization or CAD not requiring coronary revascularization) compared with oral anticoagulation monotherapy. A recent landmark clinical trial showed that rivaroxaban monotherapy significantly decreased the primary composite outcome (stroke, systemic embolism, MI, unstable angina requiring revascularization, or death from any cause) and decreased the risk of major bleeding compared with the combination therapy.<sup>1</sup> The subgroup analysis of the previously mentioned clinical trial in patients with AF only after coronary stenting and another clinical trial corroborated the main findings in a similar population.<sup>2,3</sup>

### Recommendation-Specific Supportive Text

1. An RCT compared the rivaroxaban monotherapy (n=1107) with the combination of rivaroxaban and a single APT (n=1108) in patients with AF and CCD or CAD not requiring revascularization.<sup>1</sup> The primary efficacy outcome was the composite of stroke, systemic embolism, MI, unstable angina requiring revascularization, or death from any cause. Rivaroxaban monotherapy was noninferior to dual therapy for the primary outcome (4.14% versus 5.75%/patient-year; HR, 0.72 [95% CI, 0.55-0.95]) and was superior for primary safety endpoint of major bleeding (1.62% versus 2.76%/patient-year; HR, 0.59 [95% CI, 0.39-0.89]) compared with combination therapy. Another clinical trial also showed the composite outcome of death from all causes, MI, stroke, or systemic embolism (15.7% versus 13.6%; HR, 1.16 [95% CI, 0.79-1.72];  $P=0.20$  for noninferiority); the major bleeding risk in the oral anticoagulation monotherapy group was numerically lower than the combination therapy group (7.8% versus 10.4%; HR, 0.73 [95% CI, 0.44-1.20]).<sup>2</sup> However, this trial was terminated prematurely because of slow enrollment and did not have enough power for noninferiority; thus, it was inconclusive. Of note, both clinical trials excluded patients with history of stent thrombosis. Further investigation of oral anticoagulation therapy in patients with a history of stent thrombosis is needed.

### 6.8.3. Peripheral Artery Disease (PAD)

Recommendation for PAD		
Referenced studies that support the recommendation are summarized in the Online Data Supplement.		
COR	LOE	Recommendation
2a	B-NR	1. In patients with AF and concomitant stable PAD, monotherapy oral anticoagulation is reasonable over dual therapy (anticoagulation plus aspirin or P2Y12 inhibitors) to reduce the risk of bleeding. <sup>1-5</sup>

### Synopsis

Antiplatelet monotherapy is the standard of care for patients with symptomatic PAD and reasonable in asymp-

tomatic PAD with ankle-brachial index  $\leq 0.90$  to reduce the risk of MI, stroke, and vascular death.<sup>6</sup> The 2016 AHA/ACC PAD guidelines recommend against anticoagulation for ischemic event risk reduction in the general PAD population (COR 3; LOE A) due to increased risk of bleeding without significant reduction in ischemic events compared with antiplatelet monotherapy,<sup>6,7</sup> without making specific recommendations for patients with comorbid PAD and AF. Conversely, anticoagulation is recommended for patients with AF at intermediate-to-high risk of stroke due to the inferiority of APT to prevent stroke and systemic thromboembolism in this population. Subgroup analysis of landmark DOAC clinical trials demonstrate comparable efficacy and safety of DOACs compared with warfarin among patients with AF with and without PAD.<sup>2-4</sup> Clinical trial evidence is lacking to guide decisions regarding DAT in the setting of concomitant AF and PAD (whether stable PAD or after lower extremity revascularization). Observational studies of patients with concomitant AF and PAD treated with OAC monotherapy compared with dual therapy (OAC plus antiplatelet) found an increased risk of bleeding on dual therapy without reduction in major adverse cardiac events.<sup>5,8</sup> However, an important limitation of these studies was the lack of PAD-specific outcomes such as acute or critical limb ischemia, revascularization, or amputation as primary or secondary outcomes.<sup>5,8</sup>

### Recommendation-Specific Supportive Text

1. In the WAVE (Warfarin Antiplatelet Vascular Evaluation) trial of patients with PAD but without AF, dual therapy (antiplatelet plus warfarin) did not reduce the primary outcome of MI, stroke, cardiovascular death (RR, 0.92 [95% CI, 0.73-1.16];  $P=0.48$ ) compared with monotherapy (antiplatelet alone), and dual therapy increased the risk of life-threatening bleeding (RR, 3.41 [95% CI, 1.84-6.35];  $P<0.001$ ).<sup>7</sup> Meta-analysis of 3 RCT subgroup analyses (ENGAGE AF-TIMI 48, ARISTOTLE, ROCKET AF; total N=2564) compared safety and efficacy outcomes between warfarin and DOACs in patients with concomitant AF and PAD.<sup>1-4</sup> The meta-analysis demonstrated similar efficacy for DOACs compared with warfarin, including stroke and systemic embolism (RR, 0.93 [95% CI, 0.61-1.42];  $P=0.73$ ), all-cause death (RR, 0.91 [95% CI, 0.70-1.19];  $P=0.50$ ), and MI (RR, 1.10 [95% CI, 0.64-1.90];  $P=0.74$ ), without a statistically significant difference in the risk of major bleeding (RR, 1.12 [95% CI, 0.70-1.81];  $P=0.63$ ) or ICH (RR, 0.54 [95% CI, 0.16-1.85];  $P=0.33$ ).<sup>1</sup> In ORBIT-AF II (The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II),<sup>5</sup> among AF patients with concomitant vascular disease (CAD or PAD), major adverse cardiac or neurological events and bleeding events were compared

between patients on OAC monotherapy versus dual therapy (OAC plus APT). Major adverse cardiac or neurological events (HR, 1.5 [95% CI, 1.00-2.25]) did not differ significantly between mono- and dual therapy, while dual therapy was associated with an increased risk of bleeding (HR, 2.27 [95% CI, 1.38-3.73];  $P=0.001$ ).<sup>5</sup>

**6.8.4. Chronic Kidney Disease (CKD)/Kidney Failure**

Recommendations for CKD/Kidney Failure		
Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	B-R	1. For patients with AF at elevated risk for stroke and CKD stage 3, treatment with warfarin or, preferably, evidence-based doses of direct thrombin or factor Xa inhibitors (Table 19) is recommended to reduce the risk of stroke. <sup>1-3</sup>
2a	B-NR	2. For patients with AF at elevated risk for stroke and CKD stage 4, treatment with warfarin or labeled doses of DOACs is reasonable to reduce the risk of stroke. <sup>4,5</sup>
2b	B-NR	3. For patients with AF at elevated risk for stroke and who have end-stage CKD (CrCl <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0-3.0) or an evidence-based dose of apixaban for oral anticoagulation to reduce the risk of stroke. <sup>6,7</sup>

**Synopsis**

CKD is a risk factor for stroke in patients with AF, independent of other risk factors.<sup>9</sup> The prevalence of AF among patients with renal failure on dialysis is high, including asymptomatic AF.<sup>9</sup> Despite compelling evidence in the general population, conflicting data exist as to whether AF is a risk factor for stroke in patients on dialysis.<sup>10,11</sup> Potential explanations for this discrepancy include competing risks of stroke and mortality, a high prevalence of undiagnosed AF in cohorts thought not to have AF, and the confounding effect of anticoagulation thrice weekly during hemodialysis.<sup>12</sup> VKAs are limited by a markedly reduced time in therapeutic range in patients with severe CKD, including those on dialysis,<sup>13</sup> and association with calciphylaxis.<sup>14</sup> The pivotal DOAC trials excluded patients on dialysis, and recommendations for dosing are based on pharmacokinetic data only. Early experience with dabigatran and rivaroxaban in this population suggested an increased risk of bleeding relative to warfarin, driven by the higher dose of each.<sup>15</sup> Only dabigatran is substantially removed by dialysis.<sup>16</sup> A small RCT and a retrospective population-based cohort study found a lower risk of thromboembolism with rivaroxaban versus warfarin,<sup>17,18</sup> but these findings await confirmation in larger studies. Limited data on LAAO exist in this group of patients, and prospective comparison to anticoagulation or no therapy is awaited.<sup>19</sup>

**Recommendation-Specific Supportive Text**

1. Early trials demonstrating the role of warfarin anticoagulation in preventing stroke did not enroll or

- separately report outcomes in patients with CKD. An analysis of the SPAF III trial showed that dose-adjusted warfarin, compared with fixed low-dose warfarin plus aspirin, reduced the risk of stroke with a similar magnitude to patients with normal kidney function.<sup>3</sup> In the AVERROES trial of apixaban versus aspirin in patients deemed unsuitable for warfarin, apixaban showed similar efficacy in patients with an estimated glomerular filtration rate (eGFR) of 25 to 50 mL/min as those with an eGFR >50 mL/min.<sup>20</sup> Patients with CKD stage 3, which includes those with an eGFR of 30 to 60 mL/min, were enrolled in the pivotal trials of the DOACs and showed similar results compared with warfarin as seen in patients with normal kidney function.<sup>2</sup>
2. Evidence on the use of anticoagulation in patients with AF and stage 4 CKD (eGFR, 15-30 mL/min/1.73 m<sup>2</sup>) is largely observational. A prospective, multicenter cohort study of survivors of MI with AF found that warfarin prescription at discharge associated with a reduced risk of death, readmission due to MI, ischemic stroke, and bleeding.<sup>5</sup> An analysis of patients with CrCl 25 to 30 mL/min at the time of enrollment in the ARISTOTLE trial found numerically fewer stroke and major bleeding events with apixaban than warfarin.<sup>4</sup> Because CrCl overestimates eGFR, a proportion of the patients enrolled in the pivotal clinical trials of DOACs, which used CrCl cut-offs for enrollment, had CKD stage 4 as assessed by eGFR in current clinical practice.
3. The role of anticoagulation in patients with AF and severe CKD, including those on dialysis, is controversial.<sup>6,7,21,22</sup> Pending the results of RCTs comparing warfarin with no treatment, and warfarin with DOACs, SDM incorporating risks of bleeding and thromboembolism is encouraged. The pivotal clinical trials of apixaban excluded patients with CrCl <25 mL/min.<sup>23,24</sup> Subsequently, the FDA-approved labeling was extended to include those with end-stage renal failure, including those on hemodialysis.<sup>25</sup> A subsequent pharmacokinetic study found that drug levels with apixaban 2.5 mg twice daily approximate those seen with 5 mg twice daily in patients with normal renal function, suggesting 2.5 mg is a more appropriate dose in such patients.<sup>26</sup> A large retrospective cohort study of Medicare beneficiaries found no difference in thromboembolism, but less major bleeding, in patients treated with apixaban versus warfarin.<sup>27</sup> Another analysis found an increased risk of thromboembolism and of fatal or intracranial bleeding with apixaban 5 mg twice daily versus no anticoagulation but not with apixaban 2.5 mg twice daily.<sup>28</sup> Two small trials of apixaban versus warfarin in patients with AF on hemodialysis could not show differences in safety or efficacy outcomes but significantly more bleeding than stroke events.<sup>29,30</sup>

**Table 19. Recommended Doses of Currently Approved DOACs According to Renal Function**

DOAC	CrCl (mL/min)				
	>95	51-95	31-50	15-30	<15 or on dialysis
Apixaban	5 or 2.5 mg twice daily*				
Dabigatran	150 mg twice daily	150 mg twice daily	150 mg twice daily	75 mg twice daily	Contraindicated
Edoxaban	Contraindicated	60 mg once daily	30 mg once daily	30 mg once daily	Contraindicated
Rivaroxaban	20 mg once daily	20 mg once daily	15 mg once daily	15 mg once daily	15 mg once daily†

Note that other, nonrenal considerations such as drug interactions may also apply. The gray area indicates doses not studied in the pivotal clinical trials of these agents. \*If at least 2 of the following are present: serum creatinine  $\geq 1.5$  mg/dL, age  $\geq 80$  y, or body weight  $\leq 60$  kg, the recommended dose is 2.5 mg twice daily. The ARISTOTLE trial excluded patients with either a creatinine of  $>2.5$  mg/dL or a calculated CrCl  $<25$  mL/min.

†Rivaroxaban is not recommended for other indications in patients with a CrCl  $<15$  mL/min, but such a recommendation is not made for the AF indication. However, pharmacokinetic data are limited.

AF indicates atrial fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; CrCl, creatinine clearance; and DOAC, direct oral anticoagulant.

### 6.8.5. AF in VHD

Recommendations for AF in VHD		
Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	B-R	1. In patients with rheumatic mitral stenosis or mitral stenosis of moderate or greater severity and history of AF, long-term anticoagulation with warfarin is recommended over DOACs, independent of the CHA <sub>2</sub> DS <sub>2</sub> -VASc score to prevent cardiovascular events, including stroke or death. <sup>1</sup>
1	B-NR	2. In patients with AF and valve disease other than moderate or greater mitral stenosis or a mechanical heart valve, DOACs are recommended over VKAs. <sup>2-8</sup>

### Synopsis

At least one-third of patients with AF have some degree of VHD. Patients with AF and VHD have a higher prevalence of stroke and systemic thromboembolism than those patients with AF without VHD.<sup>9</sup> Patients with VHD and AF should be evaluated for risk of thromboembolic events and treated with oral anticoagulation if they are at high risk or if they have significant mitral stenosis or a mechanical heart valve. VKAs are the anticoagulation drugs of choice for patients with rheumatic mitral stenosis, mechanical heart valves, and new-onset AF within 3 months after mechanical aortic or mitral valve surgery.<sup>10</sup>

### Recommendation-Specific Supportive Text

1. Historical data have reported that in patients with mitral stenosis and AF, stroke risk was nearly 18-fold higher than an age-, sex-, and hypertension-matched population without AF.<sup>11</sup> More recently, stroke or systemic embolism rates ranged between 0.4 and 4 per 100 patient-years among anticoagulated patients and were highest in those with previous embolism. Warfarin is generally prescribed, but it has been questioned whether a DOAC may be an alternative. A retrospective cohort study from Korea examined 2230 individuals with mitral stenosis and AF who were prescribed either warfarin or a DOAC,

using propensity matching on 10 clinical variables. Thromboembolic events in the DOAC group were 2.22% per year compared with 4.19% per year in the warfarin group (HR, 0.28 [95% CI, 0.18-0.45]).<sup>12</sup> However, in the INVICTUS (The Investigation of Rheumatic AF Treatment Using VKAs, Rivaroxaban or Aspirin Studies) RCT,<sup>1</sup> patients with AF, rheumatic heart disease, and mitral stenosis had a mean survival time to a primary outcome event of stroke, systemic embolism, MI, or death from vascular or unknown cause of 1 675 days if treated with a VKA compared with 1 599 days if with rivaroxaban (difference, -76 days [95% CI, -121 to -31];  $P < 0.001$ ).

2. Although patients with moderate to severe mitral stenosis or mechanical valve were excluded from DOAC trials, other forms of VHD were allowed, such as aortic stenosis or mitral regurgitation. Bioprosthetic valves and valve repair were allowed in the edoxaban (ENGAGE AF) and apixaban (ARISTOTLE) trials, and valve repair in the rivaroxaban (ROCKET AF) trial. A systematic review<sup>13</sup> of patients with VHD (other than moderate to severe mitral stenosis or mechanical valve) concluded that DOACs were safe. A meta-analysis confirmed that DOACs decreased the risk of stroke/systemic embolism compared with warfarin in patients with (HR, 0.70 [95% CI, 0.58-0.86]) and without VHD (HR, 0.84 [95% CI, 0.75-0.95]).<sup>14</sup> However, for patients with mechanical heart valves,<sup>15</sup> the RE-ALIGN (Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etxilate in Patients After Heart Valve Replacement)<sup>10</sup> trial was halted during phase II after enrolling 252 subjects due to increased thromboembolism and bleeding in the dabigatran arm. PROACT Xa (A Trial to Determine if Participants with an On-X Aortic Valve Can be Maintained Safely on Apixaban) was also terminated early due to higher thromboembolic events with apixaban in patients who were  $>3$  months after mechanical On-X aortic valves.

### 6.8.6. Anticoagulation of Typical AFL

Recommendations for Anticoagulation of Typical AFL* Referenced studies that support the recommendations are summarized in Online Data Supplement.		
COR	LOE	Recommendations
1	B-NR	1. For patients with AFL, anticoagulant therapy is recommended according to the same risk profile used for AF. <sup>1-3</sup>
1	C-LD	2. In patients with AFL who undergo successful cardioversion or ablation resulting in restoration of sinus rhythm, anticoagulation should be continued for at least 4 weeks postprocedure. <sup>1-4</sup>
1	A	3. Patients with typical AFL who have undergone successful CTI ablation and have had AF previously detected before AFL ablation should receive ongoing oral anticoagulation postablation as indicated for AF. <sup>5,6</sup>
1	B-NR	4. Patients with typical AFL who have undergone successful CTI ablation and are deemed to be at high thromboembolic risk, without any known previous history of AF, should receive close follow-up and arrhythmia monitoring to detect silent AF if they are not receiving ongoing anticoagulation in view of significant risk of AF. <sup>7-9</sup>
2b	B-NR	5. In patients with typical AFL who have undergone successful CTI ablation without any known previous history of AF who are at high risk for development of AF (eg, LA enlargement, inducible AF, chronic obstructive pulmonary disease [COPD], HF), it may be reasonable to prescribe long-term anticoagulation if thromboembolic risk assessment suggests high risk (>2% annual risk) for stroke. <sup>5,10-13</sup>

\*This section refers to typical right-sided (CTI-dependent) AFL. Left-sided AFLs or atrial tachycardias (ATs) that develop after ablation of AF should be anticoagulated and managed in a manner similar to AF. "Typical" AFL is defined as either typical counterclockwise AFL when the macroreentrant circuit is dependent on the CTI using the isthmus from the patient's right to left or typical clockwise AFL when the macroreentrant circuit is dependent on the CTI and uses this isthmus from the patient's left to right. "Atypical" AFL is not dependent on the CTI and may arise from a macroreentrant circuit in the LA, such as perimitral or LA roof flutter or could be dependent on scar from previous ablation or surgery.

#### Synopsis

AFL is a common atrial arrhythmia with a reported overall incidence of 88 per 100 000 person-years, and the incidence increases with age.<sup>14</sup> AFL is 2.5 times more common in men than in women, and it is significantly more likely to occur in patients with underlying HF or COPD.<sup>14</sup>

Because of the high success rate and low recurrence rate of typical AFL after CTI ablation, catheter ablation is often used as a first-line treatment. The high effectiveness of CTI ablation may decrease thromboembolic risk so that many physicians may elect to discontinue oral anticoagulation >1 month after ablation in the absence of previously detected AF. However, the high incidence of new onset AF at some time after CTI ablation places this practice in question. Because AF may be subclinical or asymptomatic, patients could be at significant risk of thromboembolic events after ablation of typical AFL depending on thromboembolic risk factors.

Catheter ablation of non-CTI-dependent AFL is technically more difficult, and "atypical" AFL or AT often occurs after AF ablation. These arrhythmias should be

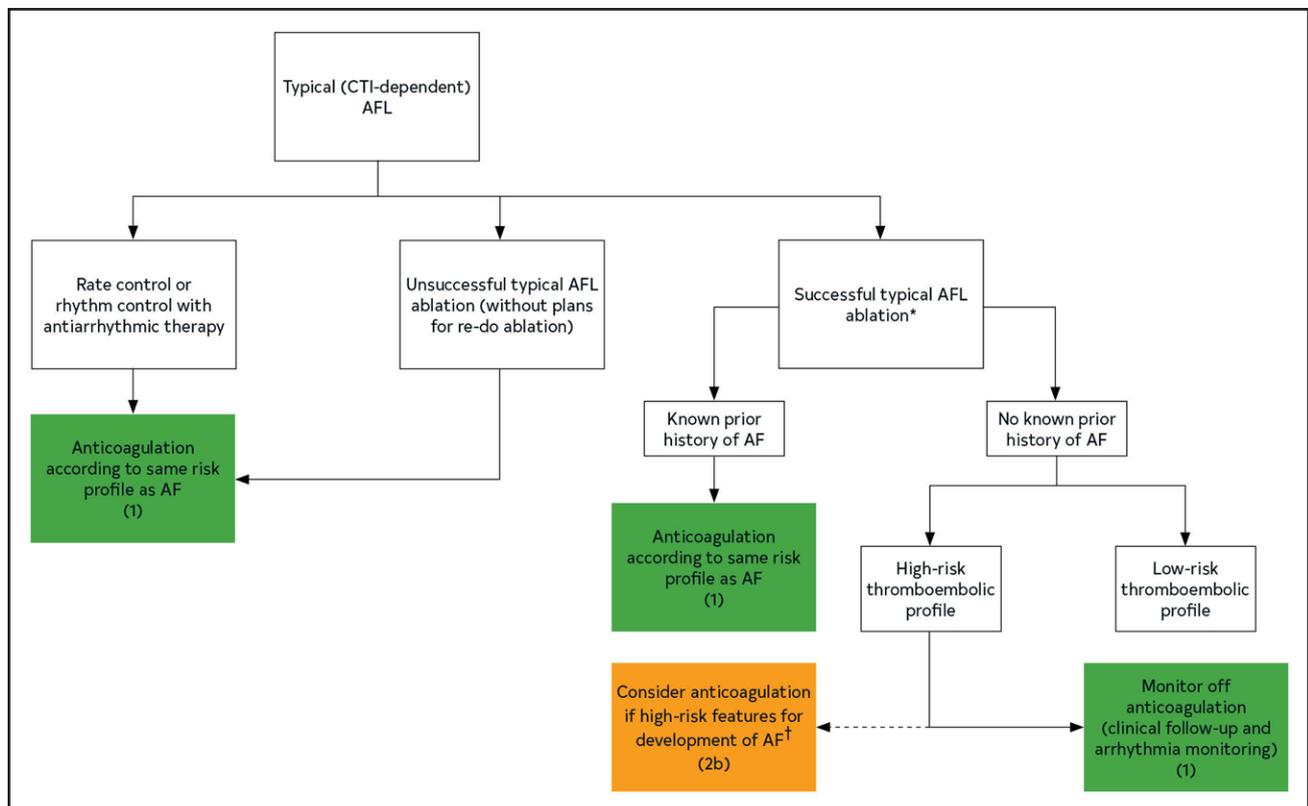
anticoagulated and managed in a manner similar to AF. Recommendations in this section refer to treatment of "typical" AFL.

#### Recommendation-Specific Supportive Text

1. AFL is associated with increased thromboembolic risk, but the exact risk and benefit of oral anticoagulation are difficult to ascertain as AFL and AF often coexist. In a population-based retrospective cohort study of patients with typical AFL and no history of AF, stroke occurred in 4.1% of patients with AFL compared with 1.2% of a general population-matched cohort ( $P<0.001$ ).<sup>1</sup> However, no large, randomized trials specifically address thromboembolic risks and benefits of anticoagulation in patients who have only AFL.

In patients referred for ablation of typical AFL without adequate previous appropriate anticoagulation, and no previous history of AF, TEE showed evidence for LA thrombus or dense spontaneous echocardiographic contrast in 3%.<sup>2</sup> A systematic review identified thromboembolic event rates of 0% to 6% with cardioversion, with the highest incidence of thromboembolic events occurring 1 to 2 days postcardioversion of AFL.<sup>3</sup> Echocardiographic studies reported LA thrombus in 0% to 38% and spontaneous echocardiographic contrast in 21% to 28% of cases.<sup>3</sup> In 1 ablation study, thromboembolic events occurred in 13.9% of patients who did not receive anticoagulation.<sup>3</sup> Observational studies report an elevated risk of stroke with AFL compared with a control group (RR, 1.4 [95% CI, 1.35-1.46]) and elevated mortality risk (risk ratio, 1.9 [95% CI, 1.2-3.1]) with long-term follow-up.<sup>3</sup>

2. The incidence of embolism after cardioversion of AFL is similar to that of AF (0.72% versus 0.46%;  $P$ =not significant).<sup>4</sup> Atrial stunning has been noted on TEE in patients undergoing cardioversion of AF, with partial atrial recovery 15 to 30 days and full recovery 30 to 90 days postcardioversion.<sup>15</sup> LAA stunning also occurs in patients with AFL, although it appears to occur at a lesser degree than what is seen with AF.<sup>16</sup> Although limited data are available for AFL, 1 study demonstrated more forceful mechanical LAA contraction and absence of spontaneous echocardiographic contrast 2 weeks after ablation of persistent AFL, suggesting earlier recovery.<sup>17</sup> Because LA and LAA stunning are thought to contribute to thrombus formation and thromboembolic events after cardioversion, continued anticoagulation is recommended early after conversion to sinus rhythm.
3. In a meta-analysis, the subsequent incidence of AF after ablation of CTI-dependent AFL was 34% over 14 months. However, the incidence of AF after flutter ablation is significantly higher in patients with



**Figure 16. Anticoagulation for Typical (CTI-Dependent) AFL**

\*Intraprocedural documentation of bidirectional block. †For example, left atrial enlargement, inducible AF, COPD, concomitant heart failure. Colors correspond to Table 2. AF indicates atrial fibrillation; AFL, atrial flutter; COPD, chronic obstructive pulmonary disease; and CTI, cavotricuspid isthmus.

a history of AF before ablation than those without AF before ablation (53% versus 23% after 16-18 months;  $P < 0.05$ ).<sup>5</sup> The incidence of AF continues to increase over time in both patients with and without previous AF.<sup>5</sup> Oral anticoagulation reduces risk of stroke or systemic thromboembolism in the setting of nonvalvular AF.<sup>6</sup> Because AF is not necessarily reduced after ablation of AFL, continued anticoagulation is recommended based on thromboembolic risk assessment. The acute success rate for catheter ablation typical AFL is reported to be 92% with a single procedure and 97% with multiple procedures in a meta-analysis.<sup>18</sup> However, the subsequent incidence of AF occurring after ablation of CTI-dependent AFL is reported to be 16% to 82%,<sup>5,10,11</sup> with a higher incidence in patients with a history of AF before ablation than those without (53% versus 23% after 16-18 months;  $P < 0.05$ ).<sup>5</sup> In 1 study, 82% of patients who underwent typical AFL ablation experienced new-onset AF during long-term follow-up (mean, 39 months).<sup>11</sup>

4. Because of the high rate of occurrence of new-onset AF after CTI ablation, close follow-up and monitoring are recommended. In patients undergoing AFL ablation, the detection of AF in patients without previous AF significantly increased with

more frequent monitoring and/or longer duration of follow-up.<sup>7</sup> This is especially important in patients at high risk of stroke or thromboembolism ( $> 2\%$ /year). Intermittent monitoring may be performed with ambulatory monitors or wearable devices. Alternatively, implantable devices can provide more prolonged and continuous monitoring. Implantable cardiac monitors have been used in multiple settings to detect AF, including after AF ablation or in patients with cryptogenic stroke. Implantable cardiac monitors have also been used for surveillance after AF ablation.<sup>9</sup>

5. Factors that predict AF after flutter ablation include LA enlargement,<sup>19-21</sup> inducible AF at the time of flutter ablation,<sup>22,23</sup> interatrial conduction time,<sup>24</sup> prolonged HV interval,<sup>25</sup> COPD,<sup>26</sup> obstructive sleep apnea,<sup>20</sup> and HATCH (hypertension, age  $\geq 75$  years, TIA or stroke, COPD, heart failure) score.<sup>21</sup> One study that reported new-onset AF in 38% of patients after AFL ablation demonstrated a thromboembolic event rate of 10% during a mean follow-up of 5 years.<sup>12</sup> In a Danish registry of patients undergoing flutter ablation, 5% of patients suffered a stroke, and 10% died during a mean follow-up of 4 years.<sup>13</sup>

Thus, patients who undergo successful flutter ablation are not free from thromboembolic

complications during long-term follow-up, likely due to a high rate of development of new-onset AF.

## 7. RATE CONTROL

### 7.1. Broad Considerations for Rate Control

Recommendations for Broad Considerations for Rate Control Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	B-NR	1. In patients with AF, SDM with the patient is recommended to discuss rhythm- versus rate-control strategies (taking into consideration clinical presentation, comorbidity burden, medication profile, and patient preferences), discuss therapeutic options, and for assessing long-term benefits. <sup>1-3</sup>
2a	B-R	2. In patients with AF without HF who are candidates for select rate-control strategies, heart rate target should be guided by underlying patient symptoms, in general aiming at a resting heart rate of <100 to 110 bpm. <sup>2,4-6</sup>

#### Synopsis

Rate control is a suitable strategy for many patients with AF.<sup>1,3</sup> A solitary randomized trial has evaluated the optimal heart rate among patients with AF. In the RACE II study (Rate Control Efficacy in Permanent Atrial Fibrillation: A Comparison Between Lenient Versus Strict Rate Control II), 614 patients with permanent AF were randomly assigned to either lenient rate control (resting heart rate <110 bpm) or strict rate control (heart rate, <80 bpm). A difference was not seen regarding either the primary composite outcome of death from cardiovascular causes, hospitalization for HF, stroke, systemic embolism, bleeding, and life-threatening arrhythmic events (absolute difference of -2.0 percentage points [90% CI, -7.6 to 3.5; *P*<0.001] for the noninferiority margin)<sup>2</sup> or the secondary outcome of QOL<sup>7</sup> at 3 years. These data suggest heart rate control intensity is not a central determinant of clinical outcomes. However, interpretation is limited by a difference of only 10 bpm between study groups attributable to the proportion of patients assigned to strict control who did not achieve target rate control (32.6%; *n*=98/301) and because 78% of lenient rate control participants having heart rate <100 bpm.<sup>8</sup> In addition, because patients with HF were underrepresented, whether the results can be extrapolated to those with HF is unknown. Nonrandomized data focused on target heart rate among outpatients,<sup>4,9,10</sup> as well as those with HF,<sup>5,11-16</sup> are divergent.

#### Recommendation-Specific Supportive Text

1. Rate- and rhythm-control strategies have comparable clinical outcomes in many patients with AF. In the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study, rate control was comparable to cardioversion and

antiarrhythmic drugs regarding survival (HR, 1.15 [95% CI, 0.99-1.34]; *P*=0.08).<sup>1</sup> In the HOT CAFE (How to Treat Chronic Atrial Fibrillation) trial, rate control was comparable to cardioversion and use of antiarrhythmic drugs with respect to a composite endpoint of all-cause mortality, number of thromboembolic events, or major bleeding (OR, 1.98 [95% CI, 0.28-22.3]; *P*>0.71).<sup>6</sup> In a meta-analysis of randomized trials and observational studies comparing rhythm with rate control, management strategies were comparable with respect to all-cause (OR, 1.34 [95% CI, 0.89-2.02]) and cardiac mortality (OR, 0.96 [95% CI, 0.77-1.20]) as well as stroke (OR, 0.99 [95% CI, 0.76-1.30]).<sup>3</sup> Although selection of a rhythm-control therapy within a year of AF diagnosis may be considered to reduce the risk of adverse cardiovascular outcomes,<sup>17</sup> early rate control may still be appropriate as a function of clinical presentation, comorbidity burden, medication profile, and patient preferences. In this context, providers should partner with their patients to select a value-concordant approach within an SDM framework.

2. In RACE II, rate-control intensity (target resting heart rate, <110 bpm versus <80 bpm) did not influence cardiovascular morbidity or mortality.<sup>6,18</sup> Rate control (AFFIRM: goal heart rate, ≤80 bpm at rest and ≤110 bpm during a 6-minute walk test; HOT CAFE: 70-90 bpm at rest and ≤140 bpm with moderate exercise) has been shown to be comparable to rhythm control in a meta-analysis of 5 trials, yet some limitation of the studies include that most patients had well-tolerated persistent AF or high risk of recurrence, no long-term follow-up, and should not be extrapolated to patients with paroxysmal AF, highly symptomatic, or patients with HF.<sup>1</sup> Observational data among outpatients and those with HF are conflicting.<sup>4</sup> In the ORBIT-AF trial, increasing heart rate was associated with higher all-cause mortality<sup>9</sup> and incident HF.<sup>10</sup> Whether a lenient rate-control strategy may be safely and effectively used in patients with heart failure with preserved ejection fraction (HFpEF)<sup>5,14</sup> or reduced fraction<sup>11-13,15,16</sup> has also shown conflicting results. Other populations that may benefit from a low heart rate goal include those with rate-related cardiac dysfunction,<sup>19</sup> ICDs,<sup>20</sup> cardiac resynchronization therapy,<sup>21</sup> and tachycardia-bradycardia form of sick sinus syndrome<sup>22</sup> (Table 20).

### 7.2. Specific Pharmacological Agents for Rate Control

The overall goals for rate control in patients with both acute and chronic AF with a rapid ventricular response center on control of symptoms and the risk of developing

**Table 20 Clinical Presentations and Objectives of Heart Rate Control**

Presentation	Objective
Symptomatic AF	To reduce symptoms
Tachycardia-induced cardiomyopathy	To improve heart function or reduce the risk of recurrent cardiomyopathy <sup>19</sup>
ICD use	To reduce risk of inappropriate shock <sup>20</sup>
Cardiac resynchronization therapy use	To enhance biventricular pacing, likelihood of myocardial recovery, and/or preservation of function <sup>21</sup>
Tachycardia-bradycardia form of sick sinus syndrome among those with a pacemaker	To reduce the risk of hospitalization <sup>22</sup>

AF indicates atrial fibrillation; and ICD, implantable cardioverter-defibrillator.

LV systolic dysfunction. In general, nondihydropyridine calcium channel blockers (diltiazem and verapamil) and beta blockers are the standard of care in rate-controlling AF. Nondihydropyridine calcium channel blockers slow conduction through the atrioventricular node and have negative inotropic and chronotropic effects. These agents are useful in ventricular rate control in the absence of preexcitation. They provide reasonable rate control and also improve AF-related symptoms compared with beta blockers.<sup>1,2</sup> Beta blockers also slow conduction through the atrioventricular node by blocking beta-1 receptors. Digoxin is a time-honored medication for patients with AF particularly among patients with HFrEF due to its positive inotropic and vagotonic effects. Limited data exist directly comparing rate-control agents, especially in the setting of long-term rate control. Selection of specific agents should consider patient-specific characteristics and response. This section will outline the principles of treatment for acute and long-term rate control.

**7.2.1. Acute Rate Control**

Recommendations for Acute Rate Control		
Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	B-R	1. In patients with AF with rapid ventricular response who are hemodynamically stable, beta blockers or nondihydropyridine calcium channel blockers (verapamil, diltiazem; provided that EF >40%) are recommended for acute rate control (Figure 17). <sup>1-4</sup>
2a	B-R	2. In patients with AF with rapid ventricular response in whom beta blockers and nondihydropyridine calcium channel blockers are ineffective or contraindicated, digoxin can be considered for acute rate control, either alone or in combination with the aforementioned agents. <sup>5-9</sup>
2a	A	3. In patients with AF with rapid ventricular response, the addition of intravenous magnesium to standard rate-control measures is reasonable to achieve and maintain rate control. <sup>10,11</sup>

Recommendations for Acute Rate Control (Continued)		
COR	LOE	Recommendations
2b	B-NR	4. In patients with AF with rapid ventricular response who are critically ill and/or in decompensated HF in whom beta blockers and nondihydropyridine calcium channel blockers are ineffective or contraindicated, intravenous amiodarone may be considered for acute rate control. <sup>12,13</sup>
3: Harm	B-NR	5. In patients with AF with rapid ventricular response and known moderate or severe LV systolic dysfunction with or without decompensated HF, intravenous nondihydropyridine calcium channel blockers should not be administered. <sup>14,15</sup>

\*Consider the risk of cardioversion and stroke when using amiodarone as a rate-control agent.

**Synopsis**

Controlling the ventricular rate in AF with a rapid ventricular response in the acute setting can vary effectiveness for control of symptoms. It can also present challenges, given some agents may or may not be preferable in the context of underlying comorbidities given the myriad of contributing factors. For patients requiring intravenous rate-control agents, hypotension and/or the presence of decompensated HF may limit use of otherwise efficacious agents. In the acute setting, recognizing patients needing emergency cardioversion is important.

**Recommendation-Specific Supportive Text**

1. A randomized, double-blind, placebo-controlled trial investigated the safety and efficacy of continuous intravenous diltiazem infusion for 24-hour heart rate control during AF and AFL. Seventeen of the 23 patients (74%) receiving diltiazem infusion and none of the 21 with placebo infusion maintained a therapeutic response for 24 hours. Over 24 hours, patients receiving diltiazem infusion lost response significantly more slowly than did those receiving placebo infusion. In another RCT, patients were randomly assigned in 1:1:1 ratio to receive intravenous diltiazem, digoxin, or amiodarone for ventricular rate control. At 24 hours, rate control was achieved in 119 of 150 patients (79%). The time to rate control was significantly shorter among patients in the diltiazem group, with the percentage of patients who achieved rate control being higher in the diltiazem group (90%) than the digoxin group (74%) and the amiodarone group (74%). A randomized, parallel, open-label study aimed to investigate esmolol versus verapamil in the acute treatment of AF or AFL. The heart rate significantly declined with esmolol and verapamil. Fifty percent of esmolol-treated patients with new onset of arrhythmias converted to sinus rhythm, whereas only 12% of those who received verapamil converted. Mild hypotension was observed in both treatment groups.
2. The use of intravenous digoxin has been shown to be effective in controlling the rate of rapid AF compared

**Table 21. Pharmacological Agents for Rate Control in Patients With AF**

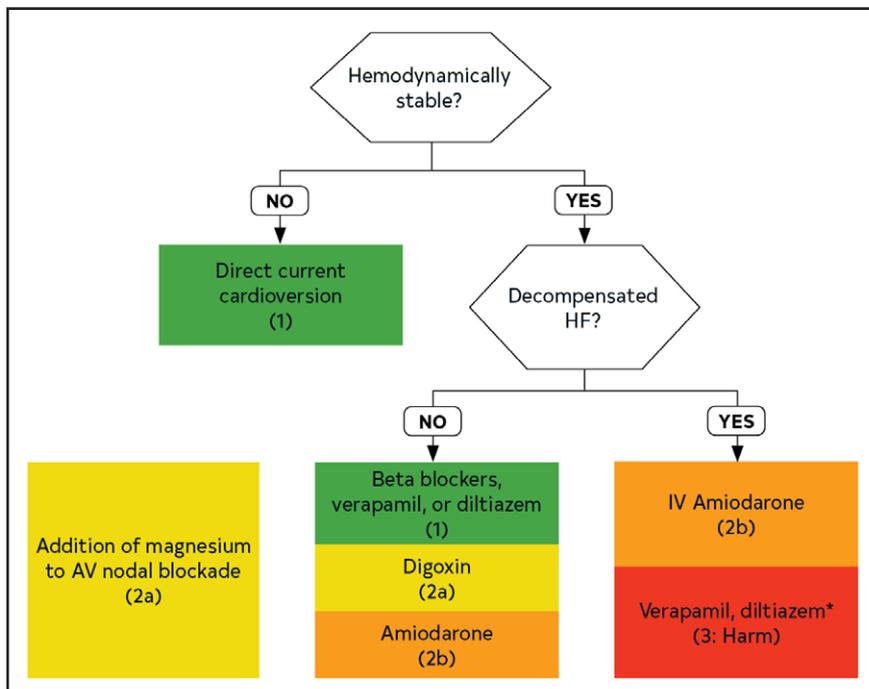
	Intravenous Administration	Oral Maintenance Dose	Elimination Half-Life	Notes
<b>Beta blockers</b>				
Metoprolol tartrate	2.5-5 mg bolus over 2 min; up to 3 doses	25-200 mg, twice daily	3-4 h	
Metoprolol succinate	N/A	50-400 mg daily or twice daily in divided doses	3-7 h	
Atenolol	N/A	25-100 mg daily	6-7 h	Renally eliminated
Bisoprolol	N/A	2.5-10 mg daily	9-12 h	
Carvedilol	N/A	3.125-25 mg, twice daily	7-10 h	
Esmolol	500 µg/kg bolus over 1 min; then 50-300 µg/kg/min	N/A	9 min	
Nadolol	N/A	10-240 mg daily	20-24 h	
Propranolol	1 mg over 1 min; repeat as needed every 2 min; up to 3 doses	10-40 mg, 3-4 times daily	IV: 2.4 h Oral: 3-6 h ER: 8-20 h	
<b>Nondihydropyridine calcium channel blockers</b>				
Diltiazem	0.25 mg/kg (actual body weight) IV over 2 min May repeat 0.35 mg/kg over 2 min; then 5-15 mg/h continuous infusion	120-360 mg daily (ER)	IV: 3-5 h Oral immediate release: 3-4.5 h ER: 4-9.5 h	Avoid in HFrEF
Verapamil	5-10 mg over ≥2 min (may repeat twice); then 5 mg/h continuous infusion (max 20 mg/h)	180-480 mg daily (ER)	IV: 6-8 h Oral: 2-7 h ER: 12-17 h	Avoid in HFrEF
<b>Digitalis glycoside</b>				
Digoxin	0.25-0.5 mg over several min; repeat doses of 0.25 mg every 6 h (maximum 1.5 mg/24 h)	0.0625-0.25 mg daily	1-2 d	Renally eliminated Increased mortality at plasma concentrations exceeding 1.2 ng/mL
<b>Other</b>				
Amiodarone	150-300 mg IV over 1 h, then 10-50 mg/h over 24 h	100-200 mg daily (generally IV form used for rate control)	IV: 9-36 d Oral: 26-107 d	Loading dose 6-10 g administered over 2-4 wk; can combine IV and oral dosing to complete

AF indicates atrial fibrillation; ER, extended release; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; and N/A, not applicable.

with placebo in 1 multicenter RCT.<sup>5</sup> However, other agents may be safer and more effective in achieving acute rate control. Intravenous diltiazem was more effective than intravenous digoxin in 2 small RCTs.<sup>6,7</sup> One trial performed at an emergency department at an academic center randomized 150 patients with AF without major comorbidities and a ventricular rate >120 bpm in a 1:1:1 ratio to intravenous diltiazem, digoxin, and amiodarone.<sup>6</sup> The time to reduce the heart rate <90 bpm was significantly shorter in the diltiazem group compared with either digoxin or amiodarone, with fewer symptoms and shorter hospital lengths of stay. Another RCT of 30 patients randomized patients with AF and a rapid ventricular response to either intravenous diltiazem, digoxin, or a combination of both agents. Treatment with intravenous diltiazem significantly decreased heart rate within 5 minutes versus 3 hours with intravenous digoxin.<sup>7</sup> Intravenous diltiazem reduced heart rate

more rapidly than intravenous digoxin in a double-blinded RCT in 40 patients with rapid AF after CABG, with similar control at 12 to 24 hours. In another RCT of 84 patients in rapid AF who presented to the emergency department, intravenous amiodarone resulted in faster control of the ventricular response compared with intravenous digoxin.<sup>8</sup> Finally, 52 patients with rapid AF were randomized to receive either an intravenous combination of diltiazem and digoxin or intravenous diltiazem alone, with a more rapid and durable response to the combination.<sup>9</sup>

- In addition to atrioventricular nodal blockers and antiarrhythmics, intravenous magnesium has been investigated for rate controlling rapid AF.<sup>10,11</sup> The mechanism likely stems from blockade of slow inward calcium channels in the sinoatrial and atrioventricular node, thereby slowing the heart rate and prolonging atrioventricular conduction velocity, respectively.<sup>16</sup> Its low adverse effect profile



**Figure 17. Acute Rate Control in AF With RVR.**

\*Contraindicated in patients with moderate-severe LV dysfunction regardless of decompensated HF. Colors correspond to Table 2. AF indicates atrial fibrillation; AV, atrioventricular; HF, heart failure; LV, left ventricular; and RVR, rapid ventricular response.

and minimal toxicity make it a favorable option, often as an adjunct to conventional therapy (ie, atrioventricular nodal blockers). A meta-analysis including 6 RCTs ( $n=745$  patients) investigated the effectiveness of intravenous magnesium in rate and rhythm control of rapid AF when administered in combination with standard rate-control methods (including beta blockers, diltiazem, verapamil, digoxin), as well as placebo. In the pooled analysis, intravenous magnesium was superior in achieving rate control (63% versus 40%; OR, 2.49 [95% CI, 1.80-3.45]) and modestly effective in rhythm conversion to sinus (21% versus 14%; OR, 1.75 [95% CI, 1.08-2.84]) compared with standard rate-control methods. Subgroup analysis showed the superiority of a lower dose ( $\leq 5$  g) (24% versus 13%; OR, 2.10 [95% CI, 1.22-3.61]) compared with the higher dose ( $>5$  g) (16% versus 13%; OR, 1.23 [95% CI, 0.65-2.32]) in rhythm control when compared with placebo.<sup>10</sup>

- Intravenous amiodarone has been shown to be effective in controlling ventricular rates in patients who are critically ill. In a retrospective study of 38 patients admitted to the intensive care unit, intravenous amiodarone was associated with a statistically significant decrease in heart rate without decrease in BP compared with intravenous diltiazem and digoxin.<sup>12</sup> One study of 60 critically ill patients, predominantly with AF, with heart rate consistently  $>120$  bpm randomized patients to 1 of 3 intravenous treatment regimens: diltiazem in a 25-mg bolus followed by a continuous infusion

of 20 mg/h for 24 hours; amiodarone in a 300-mg bolus; and amiodarone in a 300-mg bolus followed by 45 mg/h for 24 hours.<sup>13</sup> A  $>30\%$  rate reduction within 4 hours was not statistically different in either treatment arm, with less effective control more frequently observed in those receiving a bolus of amiodarone alone; thus overall, diltiazem allowed for significantly better heart rate control over 24 hours, but it also caused a significantly higher incidence of hypotension requiring discontinuation of the drug.

- Limited data exist regarding the use of nondihydropyridine calcium channel blockers in patients with HFrEF, due to the presumed limitation of negative inotropic effects. Two retrospective analyses highlight potential for increased morbidity when administered in this population. In a retrospective analysis of patients hospitalized with AF with rapid ventricular rate (RVR), diltiazem was associated with an increased risk of acute kidney injury within 48 hours of initiation of diltiazem in those patients with LVEF  $\leq 50\%$ , compared with those with normal EF (10% versus 3.6%;  $P=0.002$ ).<sup>14</sup> An additional retrospective analysis compared patients with HFrEF receiving either intravenous metoprolol or diltiazem. There was a higher incidence of worsening HF symptoms (increased oxygen requirement within 4 hours or initiation of inotropic support with 48 hours) in those patients receiving diltiazem (33% versus 15%;  $P=0.019$ ). Neither analysis noted an increase in the in-hospital mortality rate, need for a higher level of care, or hypotension.

### 7.2.2. Long-Term Rate Control

Recommendations for Long-Term Rate Control Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	B-NR	1. In patients with AF, beta blockers or nondihydropyridine calcium channel blockers (diltiazem, verapamil) are recommended for long-term rate control with the choice of agent according to underlying substrate and comorbid conditions. <sup>1,2</sup>
2a	B-NR	2. For patients with AF in whom measuring serum digoxin levels is indicated, it is reasonable to target levels <1.2 ng/mL. <sup>3-6</sup>
2a	B-R	3. In patients with AF and HF symptoms, digoxin is reasonable for long-term rate control in combination with other rate-controlling agents, or as monotherapy if other agents are not preferred, not tolerated, or contraindicated. <sup>7-9</sup>
3: Harm	C-LD	4. In patients with AF and LVEF <40%, nondihydropyridine calcium channel-blocking drugs should not be administered given their potential to exacerbate HF. <sup>10,11</sup>
3: Harm	B-R	5. In patients with permanent AF who have risk factors for cardiovascular events, dronedarone should not be used for long-term rate control. <sup>12</sup>

#### Synopsis

Both nondihydropyridine calcium channel blockers (verapamil and diltiazem) and beta blockers are effective for long-term rate control. These agents are useful in ventricular rate control in the absence of preexcitation. Digoxin may be useful in patients with limited tolerability to other agents, or as adjunct therapy in patients with a difficult to control ventricular rate. Limited data exist comparing various rate control agents, especially in the setting of chronic rate control. Selection of specific agents should consider patient-specific characteristics (ie, HFrEF, reactive airway disease) and response (Figure 18).

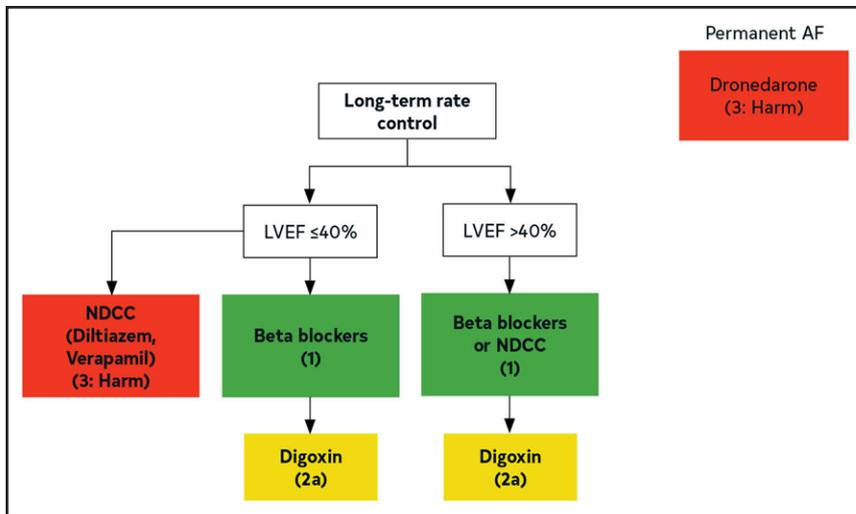
#### Recommendation-Specific Supportive Text

1. One prospective, randomized, investigator-blinded, crossover study compared the effect of 4 rate-reducing once-daily drug regimens on the ventricular heart rate and arrhythmia-related symptoms in patients with permanent AF. The 24-hour mean heart rate was 96±12 bpm at baseline (no treatment), 75±10 bpm with diltiazem, 81±11 bpm with verapamil, 82±11 bpm with metoprolol, and 84±11 bpm with carvedilol. All drugs significantly reduced the heart rate compared with baseline.<sup>13</sup> In a retrospective cohort study, investigators used a database from 2 urban emergency departments to identify consecutive patients with emergency department discharge diagnoses of AF. A total of 259 consecutive patients were enrolled, with 100 receiving calcium channel blockers and 159 receiving beta blockers. Baseline demographics and comorbidities were similar. Twenty-seven percent of patients taking beta blockers were admitted,

31.0% of patients taking calcium channel blockers were admitted, and there were no significant differences in emergency department length of stay, adverse events, or 7- or 30-day emergency department revisits. A follow-up analysis of the AFFIRM study examined the difference in all hospitalization and all-cause mortality in participants treated with a single rate-control agent at baseline. No difference was found among those participants receiving beta blockers, nondihydropyridine calcium channel blockers, or digoxin.<sup>2</sup>

2. Seminal work investigating digoxin toxicity was based on a small series of patients, where toxicity was determined by electrocardiographic abnormalities.<sup>14</sup> Toxicity was seen when serum digoxin concentrations exceeded 2.0 ng/mL, and almost certainly at levels >3.0 ng/mL. Based on this small study, the narrow therapeutic range of digoxin is usually cited as 0.8 to 2.0 ng/mL, with substantial variation across institutional laboratories and published references.<sup>15,16</sup> However, 3 post hoc analyses of the DIG (Digitalis Investigation Group) trial suggested that safe use of digoxin is seen at lower serum concentrations.<sup>4-6</sup> Serum digoxin concentrations of 0.5 to 0.9 ng/mL were associated with significantly lower all-cause mortality rates and hospitalizations compared with concentrations ≥1.0 ng/mL.<sup>3</sup> Another analysis suggested that serum digoxin concentrations >1.2 ng/mL may be harmful, particularly in women.<sup>7</sup> A post hoc analysis comparing patients with AF taking digoxin with propensity score-matched controls suggested that patients with serum digoxin concentrations <0.9 ng/mL had no increased risk of death, concentrations of 0.9 to 1.1 ng/mL had a nonsignificant increased risk of death, and serum digoxin concentrations ≥1.2 ng/mL were associated with a significant (56%) increased risk of death.<sup>4</sup> Serum digoxin concentrations of 0.5 to 0.8 ng/mL seem safest in terms of benefit without adverse effects in patients with HFrEF.<sup>17</sup>

3. Digoxin may have added efficacy as rate control in conjunction with beta blockers in patients with AF. A small RCT of 47 patients with persistent AF and concomitant HFrEF compared the effects of digoxin alone, carvedilol alone, and their combination.<sup>10</sup> Combination therapy was significantly associated with better rate control and symptom relief than monotherapy with either agent. The RATE-AF trial randomized 160 patients with persistent AF and concomitant HFrEF to digoxin and bisoprolol.<sup>11</sup> No significant differences in the primary endpoint of QOL were noted at 6 months with either agent. Several secondary outcomes, including N-terminal pro-brain natriuretic peptide level, were significantly lower in the digoxin group, without a



**Figure 18. AF Long-Term Rate Control.**

Colors correspond to Table 2. AF indicates atrial fibrillation; LVEF, left ventricular ejection fraction; and NDCC, nondihydropyridine calcium channel blocker.

significant difference in resting heart rate between the 2 groups at 12 months. Adverse effects were less common in the digoxin group. A large meta-analysis of 75 studies and approximately 620 000 patients found a significantly increased risk of death in digoxin users overall but, when limited to 7 RCTs (~8400 patients), no difference in mortality rate was observed between digoxin or placebo—of note, these 7 RCTs in the subanalysis were in patients with concomitant HF.<sup>9</sup> A post hoc sensitivity analysis assessing the impact of digoxin on mortality in patients with HF and concomitant AF found no impact on overall mortality in patients taking digoxin, most with HFrEF.

- MDPIT (Multicenter Diltiazem Postinfarction Trial) demonstrated an association of worsening HF in patients with a recent MI, with LV dysfunction randomized to diltiazem. Among those with a baseline EF of <40%, late HF appeared in significantly more patients receiving diltiazem compared with placebo (21% versus 12%;  $P=0.004$ ). Life table analysis in patients with an EF of <40% confirmed significantly more frequent late HF in those taking diltiazem. In addition, the diltiazem-associated rise in the frequency of late congestive heart failure (CHF) was progressively greater with increasingly severe decrements in baseline EF.<sup>10</sup>
- The safety and efficacy of dronedarone, originally designed as an antiarrhythmic to maintain sinus rhythm in patients with AF, was addressed in several seminal trials.<sup>18–20</sup> PALLAS (Palbociclib Collaborative Adjuvant Study) was designed to investigate whether dronedarone would reduce major vascular events or hospitalizations in patients with permanent AF. The benefits of dronedarone in patients with permanent AF were initially suggested from the ERATO (Efficacy and Safety of Dronedarone for the Control of ventricular rate during atrial fibrillation) trial, which showed a

significant reduction in the ventricular response for patients with paroxysmal and permanent AF in the 24-hour setting, which were carried forward in a 6-month follow-up.<sup>12</sup> PALLAS randomized approximately 3200 patients with permanent AF at high risk for adverse events. The trial was terminated early, because of the strong signal for harm in 43 patients receiving dronedarone versus 19 receiving placebo, namely death (13/21 due to arrhythmia), stroke, and hospitalization for HF.<sup>12</sup>

### 7.3. Atrioventricular Nodal Ablation (AVNA)

Recommendations for AVNA		
Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	C-LD	1. In patients with AF and a persistently rapid ventricular response who undergo AVNA, initial pacemaker lower rate programming should be 80 to 90 bpm to reduce the risk of sudden death. <sup>12</sup>
2a	B-R	2. In patients with AF and uncontrolled rapid ventricular response refractory to rate-control medications (who are not candidates for or in whom rhythm control has been unsuccessful), AVNA can be useful to improve symptoms and QOL. <sup>3–6</sup>
1	B-NR	3. In patients with AF who are planned to undergo AVNA, implantation of a pacemaker before the ablation (ie, before or same day of ablation) is recommended to ensure adequacy of the pacing leads before performing ablation. <sup>7–9</sup>
2b	C-LD	4. In patients with AF with normal EF undergoing AVNA, conduction system pacing of the His bundle <sup>10–13</sup> or left bundle area <sup>12,13</sup> may be reasonable.

#### Synopsis

AVNA provides ventricular rate control effectively and without medications yet creates dependence on pacing.<sup>3</sup> Consideration of the consequences of lifelong pacemaker implantation, particularly with respect to age and comorbidities, is central to decision-making regarding benefit.

Small RCTs of AVNA and right ventricular pacing (RVP) have shown improvements in symptoms and QOL compared with medical rate control alone but found no significant differences in EF or other measures of cardiac performance.<sup>3,14</sup> Progression to persistent AF is described in many patients with previously paroxysmal AF after AVNA.<sup>15,16</sup> Antiarrhythmic drugs reduce the transition to permanent AF but do not improve QOL or echocardiographic parameters, and patients treated with antiarrhythmic drugs have more episodes of HF and hospitalizations.<sup>17</sup>

Early concerns regarding AVNA included risks for device-related complications, sudden cardiac death, and worsened HF. Deaths due to malignant arrhythmias have been nearly eradicated by programming higher lower-rate pacing in the early postprocedure period.<sup>1,2,18</sup> The risks of HF may be ameliorated by non-RVP strategies, but data are limited in patients who do not have HF before AVNA.<sup>19</sup>

Overall, long-term data on outcomes after AVNA are limited, and no evidence supports AVNA as first-line therapy.<sup>9</sup>

### Recommendation-Specific Supportive Text

1. Early observational studies showed a concerning incidence of sudden death after AVNA in 3% to 7% of patients.<sup>20,21</sup> This immediate postprocedural risk results from ventricular fibrillation (VF) predominantly due to bradycardia, QT prolongation, and heterogeneity of repolarization. Initiation of VF is often pause dependent or occurs during a relatively slow pacing rate.<sup>18</sup> Deaths due to malignant arrhythmias have been minimized by current protocols specifying higher lower-rate pacing in patients after AVNA in the early postprocedure period.<sup>1,2,18</sup> Subsequent lower rate adjustment is performed over the course of several weeks.
2. AVNA and pacemaker implantation provide safe and effective rate control in the fraction of patients with AF who cannot be effectively rate controlled with medical therapy<sup>3,4,22</sup> and in whom sinus rhythm has failed or is not deemed to be effective. A meta-analysis of 6 small RCTs of studies comparing AVNA and pacemaker versus medical therapy or medical therapy with pacemaker including 323 subjects with paroxysmal or persistent AF showed improvement in symptoms and QOL in the AVNA group.<sup>6</sup> No differences in survival, stroke, hospitalization, EF, or exercise capacity were found. There was no effect of AVNA on all-cause mortality in a pooled analysis.<sup>6</sup> Nonrandomized studies have shown improvement in a range of clinical outcomes<sup>5</sup> in addition to data showing improved EF in patients with suspected tachycardia-related cardiomyopathy after AVNA.<sup>23</sup> These favorable findings in nonrandomized studies are likely subject

to the placebo effect of device implantation. Early and late complication rates are not inconsequential, specifically in young patients in view of the risk of pacemaker-mediated cardiomyopathy, and long-term follow-up data are scant.<sup>9</sup>

3. Although few studies concerning AVNA and pacing report complication rates for the pacemaker implant, the overall risk of lead dislodgement or failure is approximately 2%, and many operators perform both AVNA and pacemaker implant during the same procedure.<sup>9,13,24</sup> Practice patterns vary, however, and a European survey indicated up to 80% of operators will choose to perform AVNA 1 to 3 months after pacemaker implantation to reduce risk of adverse outcome due to early lead dislodgement.<sup>25</sup> In the prospective FOLLOWPACE registry from 23 centers in the Netherlands, lead dislodgement was the most frequent lead-related complication, occurring in 3.3% of patients within the first 2 months of implant.<sup>7</sup> Relevant to the older age population usually undergoing AVNA, a pooled patient-level analysis of 4814 subjects from CTOPP (Canadian Trial of Physiologic Pacing), UKPACE (United Kingdom pacing and cardiovascular events), and Danish pacing trials—designed to compare pacemaker implantation complication rates in age <75 years versus age ≥75 years—found a higher risk of early complications in those age ≥75 years (5% versus 3%), driven by a higher rate of lead dislodgement (2%) and pneumothorax (1.6%).<sup>8</sup> If AVNA and pacing are performed concomitantly, ideally, leads should be placed first to ensure adequate lead function.
4. HF after AVNA is attributed to the deleterious effects of RVP,<sup>26</sup> and risk is correlated with baseline cardiac function.<sup>9</sup> The PAVE (Post AV Nodal Ablation Evaluation) trial compared outcomes in patient with persistent AF and uncontrolled rates undergoing AVNA and RVP with AVNA and biventricular pacing (BiVP) and found an improvement in 6-minute walk test and EF, but benefit was predominantly seen in subjects with EF <45% or New York Heart Association (NYHA) class II to III HF at baseline.<sup>27</sup> Not all patients appear to be at high risk of HF after AVNA and RVP.<sup>28</sup> Because the benefit is less and the risk of complications is higher in BiVP compared with conventional pacing, RVP is advised in patients with preserved EF undergoing AVNA.<sup>19</sup>

Conduction system pacing of the His bundle or left bundle area offers promise to reduce the risk of RVP-induced cardiomyopathy and improve outcomes. Early studies have justifiably focused on patients with HF undergoing AVNA, and limited data are available in patients with preserved EF and no HF diagnosis.<sup>27</sup> His bundle pacing with

AVNA has been shown to be feasible and associated with improvements in EF in patients with EF <40%, and NYHA class, albeit with elevated pacing thresholds.<sup>10,11</sup> Left bundle area pacing may deliver the advantages of His bundle pacing with reduced risk of elevated pacing thresholds or lead dislodgement.<sup>12</sup> Early studies have shown stable EF with conduction system pacing and AVNA in follow-up, and improvement in patients with EF <50%.<sup>12,24</sup>

## 8. RHYTHM CONTROL

### 8.1. Goals of Therapy With Rhythm Control

Recommendations for Goals of Therapy With Rhythm Control Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	B-R	1. In patients with reduced LV function and persistent (or high burden) AF, a trial of rhythm control should be recommended to evaluate whether AF is contributing to the reduced LV function. <sup>1-6</sup>
2a	B-R	2. In patients with symptomatic AF, rhythm control can be useful to improve symptoms. <sup>7-11</sup>
2a	B-R	3. In patients with a recent diagnosis of AF (<1 year), rhythm control can be useful to reduce hospitalizations, stroke, and mortality. <sup>12-14</sup>
2a	B-R	4. In patients with AF and HF, rhythm control can be useful for improving symptoms and improving outcomes, such as mortality and hospitalizations for HF and ischemia. <sup>15-19</sup>
2a	B-NR	5. In patients with AF, rhythm-control strategies can be useful to reduce the likelihood of AF progression. <sup>20-27</sup>
2b	C-LD	6. In patients with AF where symptoms associated with AF are uncertain, a trial of rhythm control (eg, cardioversion or pharmacological therapy) may be useful to determine what if any symptoms are attributable to AF. <sup>28-32</sup>
2b	B-NR	7. In patients with AF, rhythm-control strategies may be useful to reduce the likelihood of development of dementia or worsening cardiac structural abnormalities. <sup>33-45</sup>

#### Synopsis

When caring for a patient with AF, deciding between rhythm and rate control is important but critical to acknowledge that the decision is nuanced, can evolve over time, and that the 2 strategies are necessarily not mutually exclusive depending on the definition used. For example, in EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial), which randomized patients with recently identified AF to rhythm- or rate-control strategies, in those patients randomized to the rhythm control arm, initially 87% were treated with antiarrhythmic drugs and 8% with AF ablation; but, at 2 years, 35% were not on antiarrhythmic drugs or had received AF ablation.<sup>12</sup> Similarly, although the decision on whether to use rhythm control is often based on symptoms, in a post hoc analysis of the same trial, benefits

in the composite outcome of death, stroke, or cardiac hospitalization was observed in all patients regardless of whether symptoms were present or not.<sup>30</sup> Data from EAST-AFNET 4 and large registries have consistently demonstrated the importance of monitoring patients for increased AF burden once AF has been identified and that rhythm-control therapies are more likely to be successful when implemented early when AF burden begins to increase.<sup>13,14,30,46,47</sup> Finally, for all patients with AF, continued long-term management of modifiable risk factors is essential.<sup>48</sup>

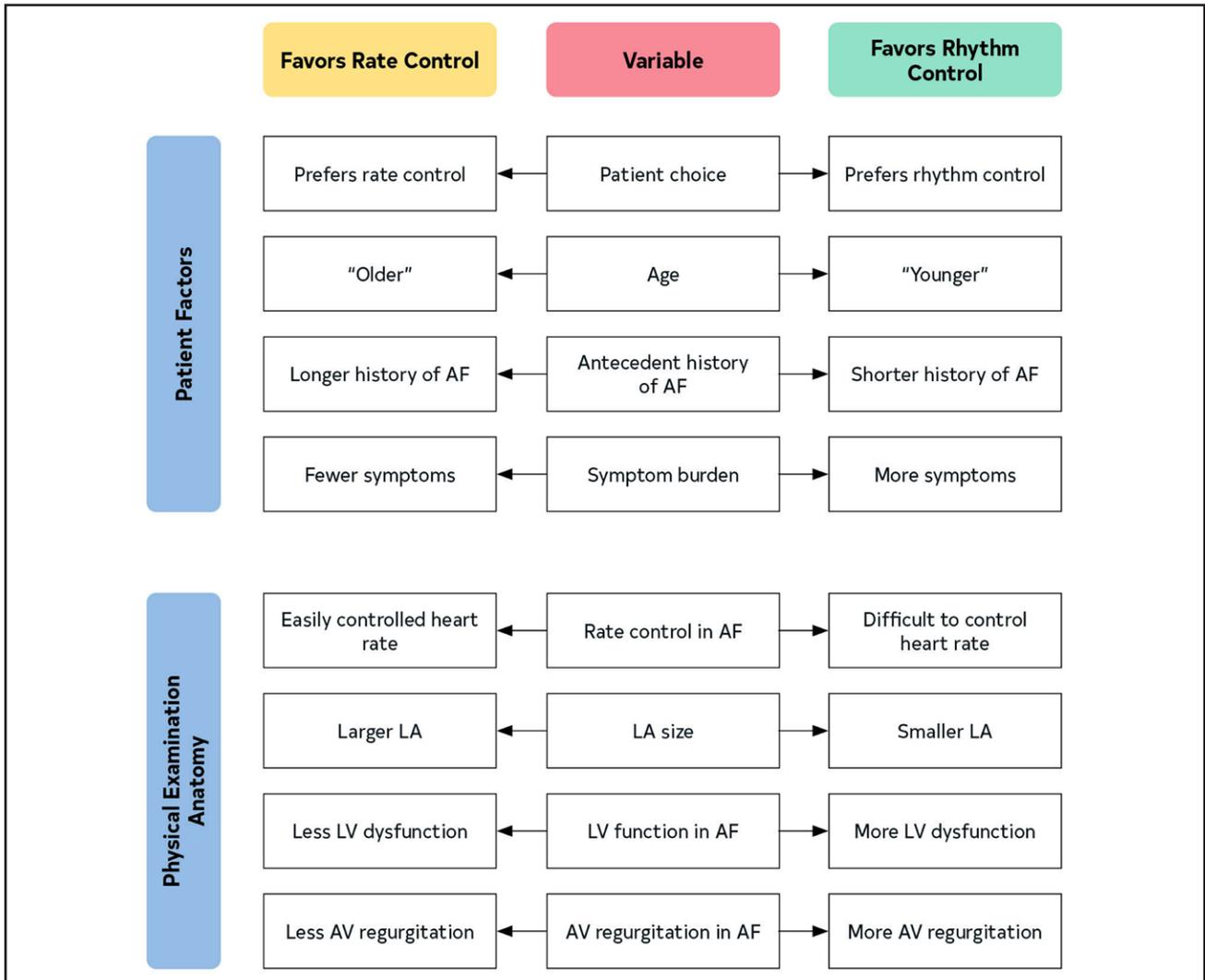
#### Recommendation-Specific Supportive Text

1. AF and reduced LV function are often recognized in the same patient, with the combination being associated with worse prognosis when compared with patients with either HF or AF alone.<sup>1,49</sup> Several studies have demonstrated improved LV function in patients with AF after restoration of sinus rhythm.<sup>2-6</sup> The incidence of AF or other atrial arrhythmias as an important contributor to reduced LVEF is unknown and likely dependent on arrhythmia burden, ventricular rates, and other factors.<sup>4-6</sup> However, in patients who present with both AF and reduced LV function or develop reduced LV function after an initial diagnosis of AF, where no identifiable cause for the reduced LV function is observed, AF should initially be assumed as a very possible cause until proven otherwise. Although AF as a cause for reduced LV function is usually considered in the setting of rapid ventricular rates, improved LV function with rhythm control has been reported in the setting of AF with relatively well controlled heart rates.<sup>2,3</sup>
2. Rhythm and rate control can improve symptoms in AF.<sup>7,8,50,51</sup> Multiple studies have shown improved QOL with rhythm control.<sup>7-9,50,51</sup> Continued symptoms due to AF are common with rate control. In the RACE II study, lenient rate control had similar primary outcomes (a combination of cardiovascular death, hospitalization for HF, and several other endpoints) compared to strict rate control, but at the end of the follow-up period (>2 years), 46% of patients in both groups had continued symptoms associated with AF.<sup>10</sup> Although a different population, symptoms due to recurrent AF were identified in 56 of 303 (18%) patients with newly identified AF undergoing rhythm control with either AADs or catheter ablation.<sup>11</sup>
3. EAST-AFNET 4 randomized 2733 patients with early onset AF (<1 year) and other risk factors for stroke to rhythm control or rate-control strategies.<sup>12</sup> Rhythm control was associated with a 25% reduction in the combined endpoint of mortality rate, stroke, and hospitalizations due to HF or ACS. In 2 observational studies, 1 from claims

data and another from a large national database, when compared with rate control, early initiation of rhythm control (<1 year) in patients with AF was associated with 15% and 19% reductions in the combined endpoint of cardiovascular death, ischemic stroke, or hospitalization for ischemia or HF, respectively.<sup>13,14</sup> However, these recent findings must be balanced against studies that have reported increased emergency department visits and health care resource utilization associated with rhythm control.<sup>52-54</sup>

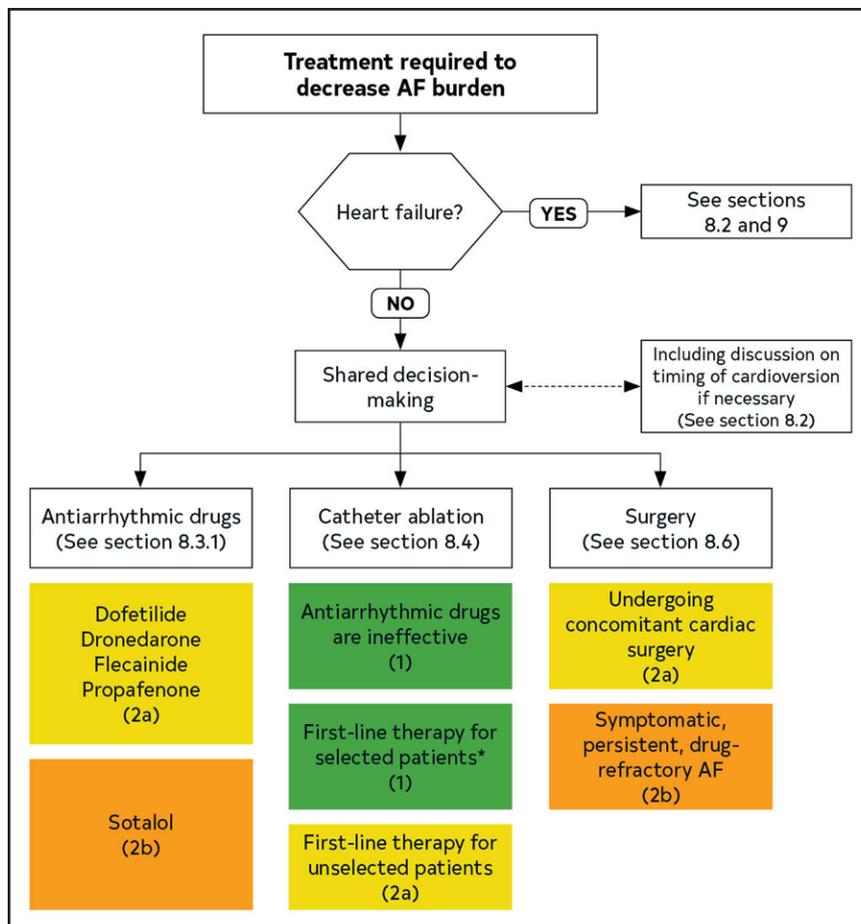
- In the AF-CHF (Atrial Fibrillation and Congestive Heart Failure) trial, rhythm control did not affect cardiovascular mortality but was associated with improved QOL.<sup>15,55</sup> Contemporary trials in patients with AF and HF, regardless of LV function, and often using catheter ablation as an important therapy, have reported trends or statistically significant improvement in clinical

outcomes associated with rhythm control when compared to rate control.<sup>16,17,49,56-58</sup> In an analysis of patients with HF in EAST-AFNET 4, rhythm control was associated with a significant reduction in the composite primary endpoint of cardiovascular death, stroke, or hospitalization due to HF or acute ischemic syndrome (HR, 0.74 [95% CI, 0.56-0.97]; *P*=0.03).<sup>16</sup> Similarly, in the CABANA (Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial, catheter ablation-based rhythm control was associated with a 46% reduction in the mortality rate in patients with HF compared with medical therapy.<sup>19</sup> Although catheter ablation is more effective in maintaining sinus rhythm than antiarrhythmic drugs, maintenance of sinus rhythm was higher in the AF-CHF trial. In this study, amiodarone was the preferential strategy for rhythm control (82% of patients) compared



**Figure 19. Patient and Clinical Considerations for Choosing Between Rhythm Control and Rate Control.**

Patient and clinical considerations for deciding between rhythm- and rate-control strategies in a patient with a high burden of AF. AF indicates atrial fibrillation; AV, atrioventricular; LA, left atrium; and LV, left ventricular.



**Figure 20. Flowchart for Treatment Choices When Required to Decrease AF Burden.**

\*Younger with few comorbidities. Colors correspond to Table 2. AF indicates atrial fibrillation.

with the ablation-based CASTLE-AF (Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation) trial (sinus rhythm at study completion: AF-CHF: 75% versus CASTLE-AF: 66%), and additionally the benefit of rhythm control in patients with HF is likely greatest in those patients with recently identified AF.<sup>15–18,49</sup>

- AF commonly, but not always, progresses over time to higher burdens and becomes more sustained.<sup>20,59</sup> Large registry studies have reported that AF progression is more commonly observed with a rate-control strategy compared to a rhythm-control strategy over a 1- to 2-year period, although the absolute magnitude and difference has varied. For example, in 2 registry studies, progression to a more sustained form of AF burden was observed in 26% to 28% of patients undergoing a rate-control strategy compared with 6% to 11% of patients treated with a rhythm-control strategy while, in an analysis of the ORBIT AF trial, although rhythm control was associated with a lower likelihood of progression, AF progression was much more common regardless of strategy (66% for rate control and 56% for rhythm control) likely due to older patients in this cohort.<sup>21–23</sup> AF

progression is a complex process, and although the choice between rhythm-control and rate-control strategy has an impact, many other factors such as age, presence or absence of HF or other comorbidities, LA size, heart rate, and modifiable risk factors are also important.<sup>21–27</sup>

- The reported prevalence of asymptomatic AF varies from 10% to 40% depending on study cohort.<sup>28</sup> Asymptomatic and symptomatic patients with AF have similar risks for death and stroke.<sup>28,29</sup> In a post hoc analysis of EAST-AFNET 4, similar magnitudes of benefit were observed in symptomatic and asymptomatic patients for reducing the combined endpoint of cardiovascular death, stroke, and hospitalization for HF.<sup>30</sup> Nevertheless, the evidence base for the benefits of a rhythm-control trial in asymptomatic patients with sinus rhythm is limited. Improved energy with return to sinus rhythm was noted in 1 observational study of 13 asymptomatic patients with persistent AF.<sup>31</sup> In another study that included 18 asymptomatic patients, at 1-month follow-up, no patients had improvement in symptoms, although sinus rhythm was maintained in only 35% of patients.<sup>32</sup> In 2 small studies that focused on the impact of catheter ablation in asymptomatic patients, maintenance of sinus rhythm was associated with

improved QOL indices in all patients, but 24% to 34% of patients developed symptoms mainly due to AT after the ablation procedure.<sup>53,54</sup>

7. AF is associated with increased cognitive impairment, progressive increase in AF burden, and structural changes in the heart.<sup>33,34</sup> Nonrandomized studies from registries or post hoc analyses of randomized trials have reported that rhythm control is associated with a reduction in the incidence of dementia and development of HF.<sup>36-38</sup> Furthermore, AF can also be an etiologic reason for mitral regurgitation or tricuspid regurgitation.<sup>39-45</sup> In 1 study of 53 patients referred for AF ablation with moderate mitral regurgitation or worse, maintenance of sinus rhythm at follow-up was associated with significant decreases in LA size, mitral annular dilatation, and mitral regurgitation.<sup>39</sup> In another study, 70% of patients undergoing ablation for AF who maintained sinus rhythm at follow-up had improvement in mitral regurgitation.<sup>40</sup> Similar results have been found in tricuspid valve function as assessed by echocardiography.<sup>42-45</sup>

## 8.2. Electrical and Pharmacological Cardioversion

Cardioversion to restore sinus rhythm is a mode of acute rhythm control. Cardioversion can be achieved electrically or pharmacologically. Electrical cardioversion, given rapidity and efficacy, is the treatment of choice for patients with hemodynamic instability attributable to AF. Acute rhythm control with cardioversion should also be considered for patients with hemodynamically stable AF intolerant of atrioventricular dyssynchrony, loss of atrial kick, or unable to achieve adequate rate control. In patients with hemodynamically stable AF, both electrical cardioversion and pharmacological cardioversion are acceptable, safe, and efficacious methods for acute rhythm control.<sup>1-3</sup> Electrical cardioversion is more effective than pharmacological cardioversion alone<sup>4,5</sup> but involves the trade-off of anesthesia or sedation.<sup>6</sup> Thromboembolic risks and considerations for anticoagulation apply to both pharmacological cardioversion and electrical cardioversion.<sup>78</sup>

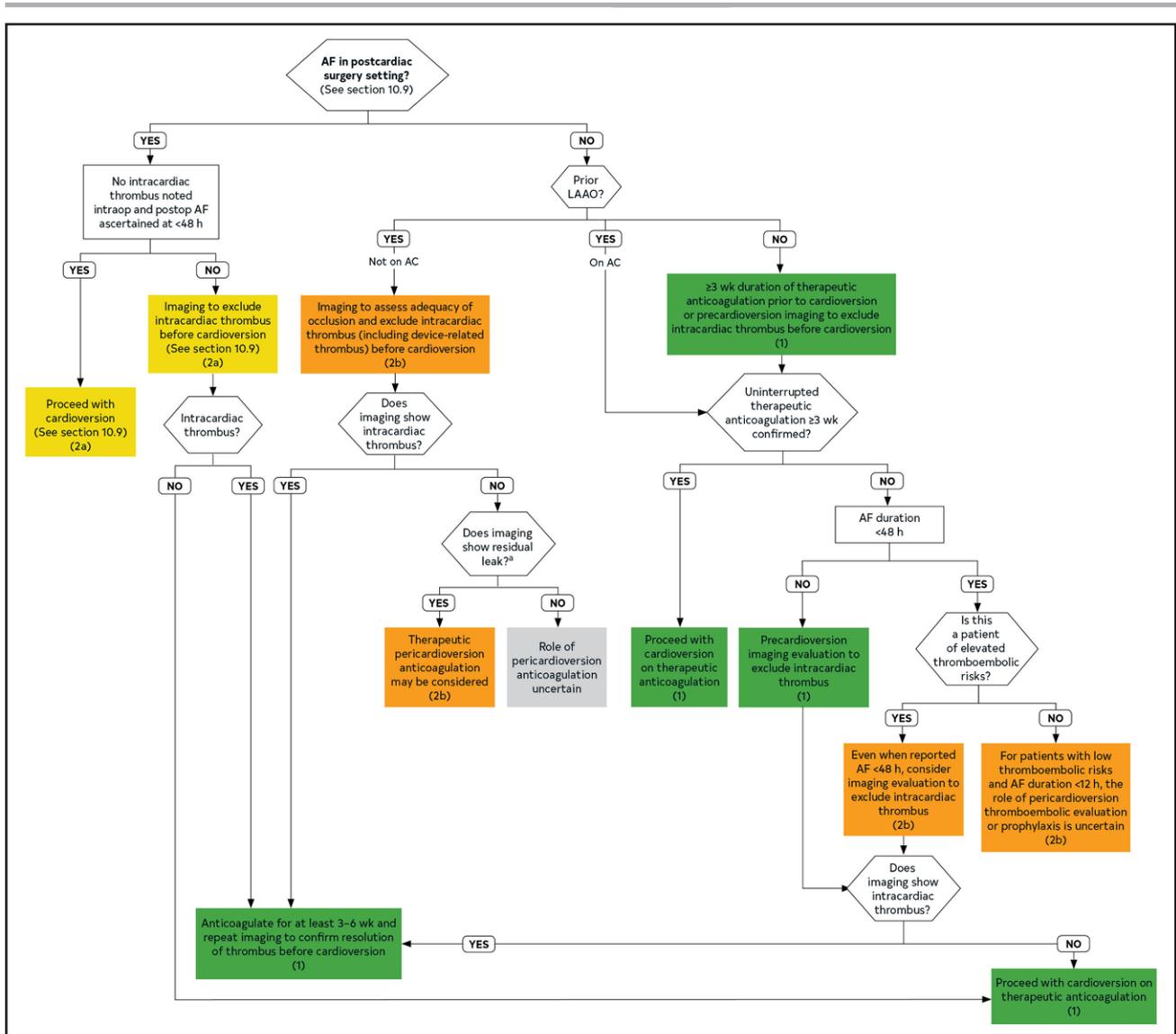
### 8.2.1. Prevention of Thromboembolism in the Setting of Cardioversion

Recommendations for Prevention of Thromboembolism in the Setting of Cardioversion		
Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	B-R	1. In patients with AF duration of ≥48 hours, a 3-week duration of uninterrupted therapeutic anticoagulation or imaging evaluation to exclude intracardiac thrombus is recommended before elective cardioversion. <sup>1</sup>

Recommendations for Prevention of Thromboembolism in the Setting of Cardioversion (Continued)		
COR	LOE	Recommendations
1	B-NR	2. In patients with AF undergoing cardioversion, therapeutic anticoagulation should be established before cardioversion and continued for at least 4 weeks afterwards without interruption to prevent thromboembolism. <sup>2-7</sup>
1	C-LD	3. In patients with AF in whom cardioversion is deferred due to LAA thrombus detected on precardioversion imaging, therapeutic anticoagulation should be instituted for at least 3 to 6 weeks, after which imaging should be repeated before cardioversion. <sup>1,8</sup>
2b	B-NR	4. In patients with AF and previous LAAO who are not on anticoagulation, imaging evaluation to assess the adequacy of LAAO and exclude device-related thrombosis before cardioversion may be reasonable. <sup>9-19</sup>
2b	C-LD	5. In patients with AF and previous LAAO with residual leak, pericardioversion anticoagulation may be considered and continued thereafter. <sup>9-11,20</sup>
2b	C-LD	6. In patients with reported AF duration of <48 hours (not in the setting of cardiac surgery) and who are not on anticoagulation, precardioversion imaging to exclude intracardiac thrombus may be considered in those who are at elevated thromboembolic risk (CHA <sub>2</sub> DS <sub>2</sub> -VASc score ≥2 or equivalent). <sup>21,22</sup>
2b	C-LD	7. In patients with low thromboembolic risks (CHA <sub>2</sub> DS <sub>2</sub> -VASc 0-1 or equivalent) and AF duration of <12 hours, the benefit of precardioversion imaging or pericardioversion anticoagulation is uncertain given the low incidence of pericardioversion thromboembolic events in this population. <sup>21,22</sup>

### Synopsis

Thromboembolic risks and considerations of anticoagulation apply to both pharmacological cardioversion and electrical cardioversion.<sup>23,24</sup> Thromboembolic risks in the setting of acute cardioversion relate to preexisting thrombus, change in atrial mechanical function with restoration of sinus rhythm, atrial stunning postcardioversion, and transient prothrombotic state.<sup>2,25</sup> DOACs are alternatives to VKAs as thromboprophylaxis in the setting of cardioversion.<sup>26-29</sup> Given additional favorable attributes of rapid time to therapeutic efficacy, reliability of maintenance of therapeutic efficacy, and ease of continuation, DOACs may be preferentially considered over VKAs for patients with AF planned for cardioversion barring contraindications to DOAC therapy. Precardioversion imaging is prudent for patients with AF who have previously undergone LAAO and are not on anticoagulation.<sup>9,10,14-16,19</sup> Thromboembolic risks for patients with <48 hours of AF were not homogenous but, rather, varied by a patient's risk profile for thromboembolic complications (as defined by risk scores in specific studies) and duration of AF.<sup>21,22</sup> More nuanced consideration of a patient's thromboembolic risks in the setting of cardioversion for AF may integrate a patient's substrate for atrial myopathy and risks for thromboembolism instead of strict dependence on the previously used 48-hour duration threshold.



**Figure 21. Patients With Hemodynamically Stable AF Planned for Cardioversion.**

Colors correspond to Table 2. AC indicates anticoagulation; AF, atrial fibrillation; and LAAO, left atrial appendage occlusion.

**Recommendation-Specific Supportive Text**

1. Early experience with both pharmacological and then electrical cardioversion of AF led to the observation that thromboembolism was less frequent in patients who were chronically anticoagulated than those who were not.<sup>30</sup> This led to an empiric recommendation for 3 weeks of anticoagulation before cardioversion in the prospective, randomized, multicenter ACUTE (Assessment of Cardioversion Using Transesophageal Echocardiography) study of patients with >2 days' duration of AF.<sup>31</sup> Preadioversion anticoagulation of at least 3 weeks may be accomplished via either therapeutic anticoagulation with VKAs or DOACs.<sup>26-28</sup> Cardiac computed tomography, particularly with delayed contrast-enhanced image acquisition protocol, has emerged as an alternate imaging modality to exclude intracardiac thrombus.<sup>32-34</sup>

2. Rationales for establishment of therapeutic anticoagulation before cardioversion and continuation for the subsequent 4 weeks after cardioversion for AF are driven by elevated thromboembolic risks,<sup>6,7,35</sup> high early recurrence of AF,<sup>36</sup> and observation of atrial dysfunction<sup>2-5</sup> during this period. Thromboembolic risks are elevated around the time of cardioversion, especially within the 30 days after cardioversion.<sup>6,7</sup> The observation of spontaneous echocardiographic contrast in association with atrial dysfunction on TEE after cardioversion raised mechanistic concerns for atrial stunning in the setting of cardioversion,<sup>2,3</sup> with recovery of mechanical atrial systole over the ensuing 1 month.<sup>4,5</sup> Rapidity of recovery of mechanical atrial systole may be influenced by clinical variables,<sup>37</sup> duration of the antecedent AF episode leading to cardioversion,<sup>5</sup>

- and the extent of comorbid conditions as risks factors for atrial myopathy.<sup>38</sup>
3. In patients with AF, detection of intracardiac thrombus should prompt cancellation of planned cardioversion and institution of therapeutic anticoagulation in anticoagulant-naïve patients. Detection of intracardiac thrombus in patients already on anticoagulation should prompt assessment of compliance, dosing appropriateness, drug absorption, and drug interactions. In patients with thrombus detected despite already being anticoagulated, potential reasons should be investigated, such as nonadherence and drug interaction, which may cause subtherapeutic levels. Switching to an alternate anticoagulant can be considered, although the benefit is uncertain. In anticoagulant-naïve patients, 61.2% had resolution of thrombus on follow-up TEE performed 3 to 12 weeks after initiation of VKA in the CLOT-AF (Retrospective Registry Providing Baseline Data on the Outcome of Left Atrial [LA] or LA Appendage [LAA] Thrombus in Patients With Nonvalvular Atrial Fibrillation [AF] or Atrial Flutter After Standard of Care [SoC] Anticoagulant Therapy) study, and 41.5% had resolution of thrombus on follow-up TEE performed 6 weeks after therapy with rivaroxaban in the X-TRA (Exploring the Efficacy of Once Daily Oral Rivaroxaban for Treatment of Thrombus in Left Atrial/Left Atrial Appendage in Subjects With Nonvalvular Atrial Fibrillation or Atrial Flutter) study.<sup>8</sup> Repeat imaging (TEE or computed tomography<sup>32-34</sup>) is generally pursued after at least 3 to 6 weeks of therapeutic anticoagulation to assess for resolution of intracardiac thrombus before reconsidering cardioversion.<sup>1,8</sup>
  4. In the subset of patients who have undergone surgical or pLAAO procedures, inadequate occlusion may be seen acutely during the procedure or delayed after the procedure.<sup>9-14</sup> Inadequate LAAO has been associated with elevated risks for thromboembolism.<sup>9-11</sup> Device-related thrombosis, reported in patients with pLAAO devices,<sup>15-19</sup> has also been associated with elevated stroke/systemic embolism.<sup>15-18</sup> Imaging with TEE or cardiac computed tomography can assess adequacy of LAAO, residual leak, and device-related thrombosis.<sup>39-41</sup> In the setting of transesophageal echocardiographic imaging before electrical cardioversion, device-related thrombus was detected in 2.7% (4 of 148 patients) of a small multicenter retrospective analysis of patients with Watchman LAAO device.<sup>20</sup> These 4 patients were treated with oral anticoagulation and after 6 to 8 weeks, on confirmation of thrombus resolution by repeat TEE, underwent successful electrical cardioversion.<sup>20</sup>
  5. Data are limited to guide pericardioversion anticoagulation in patients with LAAO. In the broader (not limited to cardioversion) context, residual leak  $\leq 5$  mm by computed tomography after LAAO by surgical ligation has been associated with particularly elevated stroke/system embolism risks (especially in the absence of anticoagulation)<sup>9</sup> and similarly for residual leak  $< 5$  mm by TEE post-Lariat.<sup>10</sup> A large analysis that stratified National Cardiovascular Data Registry LAAO registry Watchman 2.5 device patients by transesophageal echocardiographic observation of residual leak (none,  $\leq 5$  mm,  $> 5$  mm) at 45 days, found  $\leq 5$  mm residual leak to be common (13 258 of 51 333 patients; 25.8%) and associated with modestly higher incidence of thromboembolic events over 1-year follow-up compared with no leak.<sup>11</sup> OAC use was more frequent in patients with large ( $> 5$  mm) residual leak.<sup>11</sup> Data specific to the setting of cardioversion are further limited. The largest to date is a retrospective multicenter study of 148 Watchman LAAO device patients who underwent electrical cardioversion after precardioversion exclusion of intracardiac thrombus or large residual leak ( $\geq 5$  mm in this study) by TEE.<sup>20</sup> No thromboembolic events were observed within 6 weeks of cardioversion, in recipients or nonrecipients of pericardioversion anticoagulation.<sup>20</sup> However, detection of thromboembolic events may be limited by study's sample size. Pericardioversion antithrombotic regimen was at the discretion of the treating physicians,<sup>20</sup> and the relationship of anticoagulation with presence/absence of small residual leak was not reported. Considerations for anticoagulation may also vary based on specific surgical or pLAAO procedures and devices.
  6. The safety of cardioversion without further assessment or previous anticoagulation in patients with AF duration of  $< 48$  hours has been challenged. In addition to concerns for underestimation of actual duration of episode and burden due to potential for asymptomatic occurrence of AF, emerging data demonstrate that thromboembolic risks in patients with  $< 48$  hours of AF were not homogeneously low. Time to cardioversion  $> 12$  hours has been reported as an independent predictor for thromboembolic complications.<sup>21</sup> A single-center observational study of patients undergoing cardioversion for AF of  $< 48$  hours duration did not observe thromboembolic events in patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 or 1 or patients with postoperative AF but noted differential thromboembolic rates in CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$ .<sup>42</sup> Larger studies similarly demonstrated that among patients with  $< 48$  hours of AF, postcardioversion thromboembolic risks increased with increasing CHA<sub>2</sub>DS<sub>2</sub>-VASc

score,<sup>22,43</sup> especially in those with CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  in the absence of anticoagulation.<sup>22</sup>

- Retrospective observational data from the FinCV (Finnish CardioVersion) study noted low incidence of 30-day pericardioversion thromboembolic event rate of 0.4% in patients with AF with CHA<sub>2</sub>DS<sub>2</sub>-VASc of 0 to 1<sup>22</sup> or 0.3% in patients with duration of <12 hours of AF.<sup>21</sup> Other retrospective studies have similarly demonstrated low pericardioversion thromboembolic risks in patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 to 1.<sup>42</sup> The combination of CHA<sub>2</sub>DS<sub>2</sub>-VASc of 0 to 1 in conjunction with duration of <12 hours of AF may identify a population at particularly low risk for pericardioversion thromboembolism.

### 8.2.2. Electrical Cardioversion

Recommendations for Electrical Cardioversion Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	C-LD	1. In patients with hemodynamic instability attributable to AF, immediate electrical cardioversion should be performed to restore sinus rhythm. <sup>1</sup>
1	B-R	2. In patients with AF who are hemodynamically stable, electrical cardioversion can be performed as initial rhythm-control strategy or after unsuccessful pharmacological cardioversion. <sup>2</sup>
1	C-LD	3. In patients with AF undergoing electrical cardioversion, energy delivery should be confirmed to be synchronized to the QRS to reduce the risk of inducing VF. <sup>3</sup>
2a	B-R	4. For patients with AF undergoing elective electrical cardioversion, the use of biphasic energy of at least 200 J as initial energy can be beneficial to improve success of initial electrical shock. <sup>4,5</sup>
2a	B-NR	5. In patients with AF undergoing elective cardioversion, with longer duration of AF or unsuccessful initial shock, optimization of electrode vector, use of higher energy, and pretreatment with antiarrhythmic drugs can facilitate success of electrical cardioversion. <sup>5-9</sup>
2b	C-LD	6. In patients with obesity and AF, use of manual pressure augmentation and/or further escalation of electrical energy may be beneficial to improve success of electrical cardioversion. <sup>10</sup>

#### Synopsis

Electrical cardioversion is a strategy for acute rhythm control. Compared with pharmacological cardioversion alone, electrical cardioversion with synchronized direct current cardioversion is more rapid and efficacious for restoring sinus rhythm from AF.<sup>1,11,12</sup> Given rapidity and efficacy, electrical cardioversion is the treatment of choice for patients with hemodynamically unstable AF.

In hemodynamically stable patients with AF planned for acute rhythm control, electrical cardioversion can be performed as an initial strategy or after unsuccessful pharmacological cardioversion.<sup>2,6,13,14</sup> Electrical cardioversion is favored over pharmacological cardioversion when the patient is able to tolerate sedation, desires

more immediate rhythm conversion, or has failed or not met candidacy for pharmacological cardioversion.

Although electrical cardioversion may achieve acute restoration of sinus rhythm, durability of sinus rhythm may be influenced by ongoing acute conditions, LA size, duration of the history of AF and/or specific episode, and comorbidities.<sup>14</sup> In patients with a longer duration of AF, immediate recurrence of AF, a previous unsuccessful electrical cardioversion, or a desire to employ all reasonable efforts to avoid an AF recurrence, pretreatment antiarrhythmic drugs and subsequent continuation to facilitate success of acute cardioversion and promote maintenance of sinus rhythm postcardioversion<sup>6,8,9</sup> may be pursued in the context of SDM with the patient. Optimization of energy delivery, electrode vector, and reduction of transthoracic impedance with manual pressure augmentation may also improve success of electrical cardioversion.<sup>5-10</sup>

#### Recommendation-Specific Supportive Text

- In patients with hemodynamically unstable AF, immediate electrical cardioversion with synchronized direct current cardioversion is the treatment of choice. Direct data on emergency cardioversion of hemodynamically unstable patients is limited because of the emergency circumstances of the clinical context. Data on direct current cardioversion of AF in hemodynamically stable patients demonstrate high success rate of restoring sinus rhythm with direct current cardioversion.<sup>1,11,15-18</sup> Electrical cardioversion is rapid. Electrical cardioversion alone is more effective than pharmacological cardioversion alone.<sup>1,11,12</sup>
- Goals of rhythm control are summarized in **Section 8.1 (“Goals of Therapy With Rhythm Control”)**. Real-world data support both electrical cardioversion and pharmacological cardioversion as acceptable, safe, and efficacious methods for acute rhythm control.<sup>6,13,14</sup> Electrical cardioversion is more effective than pharmacological cardioversion alone<sup>1,11</sup> but involves the trade-off of requiring sedation.<sup>19</sup> In patients with hemodynamically stable AF of recent onset, the RAFF2 (Electrical versus pharmacological cardioversion for emergency department patients with acute atrial fibrillation) study demonstrated high success of restoration of sinus rhythm with either an upfront electrical cardioversion strategy or a stepwise strategy with initial pharmacological cardioversion and then direct current cardioversion if the pharmacological intervention did not restore sinus rhythm.<sup>2</sup> In patients with unsuccessful pharmacological cardioversion, instead of switching to another antiarrhythmic drug (and with concerns for potentiation of adverse effects such as QT prolongation or bradycardia), electrical cardioversion should be pursued as next

step for acute rhythm control. Therefore, in patients with hemodynamically stable AF, electrical cardioversion is favored over pharmacological cardioversion when the patient is able to tolerate sedation, desires more immediate rhythm conversion, or has failed or not met candidacy for pharmacological cardioversion. Monitoring and preparedness during and after electrical cardioversion include monitoring for rare chronotropic, hemodynamic, or thromboembolic complications, and the effects of anesthesia administered during electrical cardioversion.<sup>6,13,14,20–22</sup>

3. Unsynchronized or inappropriately synchronized cardioversion can induce VF if the shock energy is delivered during the vulnerable period, the inscription of the T wave.<sup>3,23–25</sup> Therefore, electrical cardioversion for AF should be synchronized with the QRS complex. The synchronization feature needs to be turned on or confirmed that it is on; in patients who require multiple shocks, the synchronization feature must be manually activated and/or confirmed before each shock attempt. Visual confirmation of synchronization to QRS is important to detect inappropriate synchronization and ensure appropriate synchronization.
4. An earlier small, multicenter, prospective randomized study demonstrated higher efficacy of initial electrical cardioversion with a biphasic waveform instead of monophasic waveform.<sup>4</sup> A more contemporary single-centered, randomized study of 279 patients who were randomized to synchronized direct current cardioversion with biphasic waveform with either upfront maximum-fixed energy or strategy of low-escalating energy found higher first shock success with maximum-fixed energy (75% compared with 34% for low-escalating energy group).<sup>5</sup> In the contemporary RAFF2 study of patients with hemodynamically stable AF of recent onset, the upfront electrical cardioversion group with initial biphasic 200 J shock (and up to 3 consecutive shocks allowed, with higher energy permitted for subsequent shocks) had conversion to sinus rhythm in 176 of 192 (92%) patients in this upfront electrical cardioversion shock-only group.<sup>2</sup>
5. A previous study of patients with persistent AF (median AF duration, 5 months) undergoing direct current cardioversion with escalation of energy found the anterior-posterior orientation of the electrode vector more successful at restoring sinus rhythm than an anterior-lateral vector,<sup>7</sup> while a subsequent study of patients with recently diagnosed AF (≥3 hours and <7 days) undergoing direct current cardioversion using biphasic upfront 200 J showed similar success rates with electrode vectors in either anterior-posterior or anterior-lateral orientation.<sup>2</sup> Taken together, when energy output

is optimized as biphasic and maximal output and the AF is of recent onset, either vector orientation may be reasonable, but for patients with longer duration of AF, the anterior-posterior orientation of electrode vector may be favorable.<sup>2</sup> Manual pressure augmentation<sup>26</sup> or administration of antiarrhythmic drugs as pretreatment (**Section 8.2.3, “Pharmacological Cardioversion”**)<sup>6,8,9</sup> may also facilitate electrical cardioversion.

6. Increased body weight has been associated with reduced success of electrical cardioversion.<sup>27</sup> In a small randomized clinical study, use of paddles, manual pressure augmentation (using electrically silent objects as insulator), and further escalation of electrical energy improved success of electrical cardioversion of obese patients with AF,<sup>10</sup> and the benefits of these maneuvers may mechanistically relate to overcoming increased transthoracic impedance. Other alternatives in refractory cases include the use of 2 defibrillators simultaneously, effectively doubling the delivered energy.

### 8.2.3. Pharmacological Cardioversion

Recommendations for Pharmacological Cardioversion		
Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
2a	C-LD	1. For patients with AF, pharmacological cardioversion is reasonable as an alternative to electrical cardioversion for those who are hemodynamically stable or in situations when electrical cardioversion is preferred but cannot be performed. <sup>1</sup>
2a	A	2. For patients with AF, ibutilide <sup>2,3</sup> is reasonable for pharmacological cardioversion for patients without depressed LV function (LVEF <40%).
2a	A	3. For patients with AF, intravenous amiodarone is reasonable for pharmacological cardioversion, although time to conversion is generally longer than with other agents (8–12 hours). <sup>4–8</sup>
2a	A	4. For patients with recurrent AF occurring outside the setting of a hospital, the “pill-in-the-pocket” (PITP) approach with a single oral dose of flecainide <sup>9–11</sup> or propafenone, <sup>10–14</sup> with a concomitant atrioventricular nodal blocking agent, <sup>15</sup> is reasonable for pharmacological cardioversion if previously tested in a monitored setting. <sup>16–18</sup>
2b	B-R	5. For patients with AF, use of intravenous procainamide may be considered for pharmacological cardioversion when other intravenous agents are contraindicated or not preferred. <sup>19</sup>

#### Synopsis

Pharmacological cardioversion is indicated for patients with new-onset or persistent AF that is hemodynamically stable, or in rare instances when electrical cardioversion is desired but contraindicated. Ibutilide works rapidly for pharmacological cardioversion of AF but is associated with QT interval prolongation and torsades de pointes, particularly in patients with HFrEF.<sup>2,3,20,21</sup> Data support intravenous amiodarone for pharmacological

**Table 22. Drugs for Pharmacological Conversion of AF to Sinus Rhythm**

Drug	Route of Administration	Loading Dose	Maintenance Dose	Approximate Time to Conversion to Sinus Rhythm	Primary Route(s) of Elimination	Elimination Half-Life	Major Adverse Effects
Amiodarone	IV	5-7 mg/kg or 300 mg*	1200-3000 mg via continuous infusion over 24 h	8-12 h	Liver metabolism Biliary excretion	9-36 d	Bradycardia Hypotension QT prolongation Phlebitis TdP
Flecainide	Oral†	200 mg if <70 kg, 300 mg if >70 kg, single dose	N/A	3-8 h	Liver (70%) Kidney (30%)‡	12-27 h	Atrial flutter AV block Dizziness Dyspnea Exacerbation of HFrEF Headache Nausea QT prolongation VT Visual disturbances
Ibutilide	IV	≥60 kg: 1 mg over 10 min <60 kg: 0.01 mg/kg over 10 min If arrhythmia does not terminate within 10 min after the end of the first infusion, may administer a second dose, equal to the first dose.	N/A	30-90 min	Liver	2-12 h	Nonsustained VT QT prolongation TdP
Procainamide	IV	1 g over 30 min	2 mg/min continuous infusion over 1 h	30-60 min	Liver (16-33%) Kidney (50-65%)‡	3-4 h (parent) 7 h (NAPA)	Agranulocytosis AV block Exacerbation of HFrEF Hypotension Neutropenia QT prolongation Rash Thrombocytopenia TdP
Propafenone	Oral	450 mg if <70 kg, 600 mg if >70 kg, single dose	N/A	3-8 h	Liver	9 h	Atrial flutter AV block Dizziness Dyspnea Exacerbation of HFrEF Nausea Taste disturbances VT Visual disturbances

\*Some studies have administered intravenous amiodarone for 24 h followed by oral administration.

†Flecainide is available in an intravenous dosage form in Europe.

‡Percentage of a dose excreted unchanged in urine.

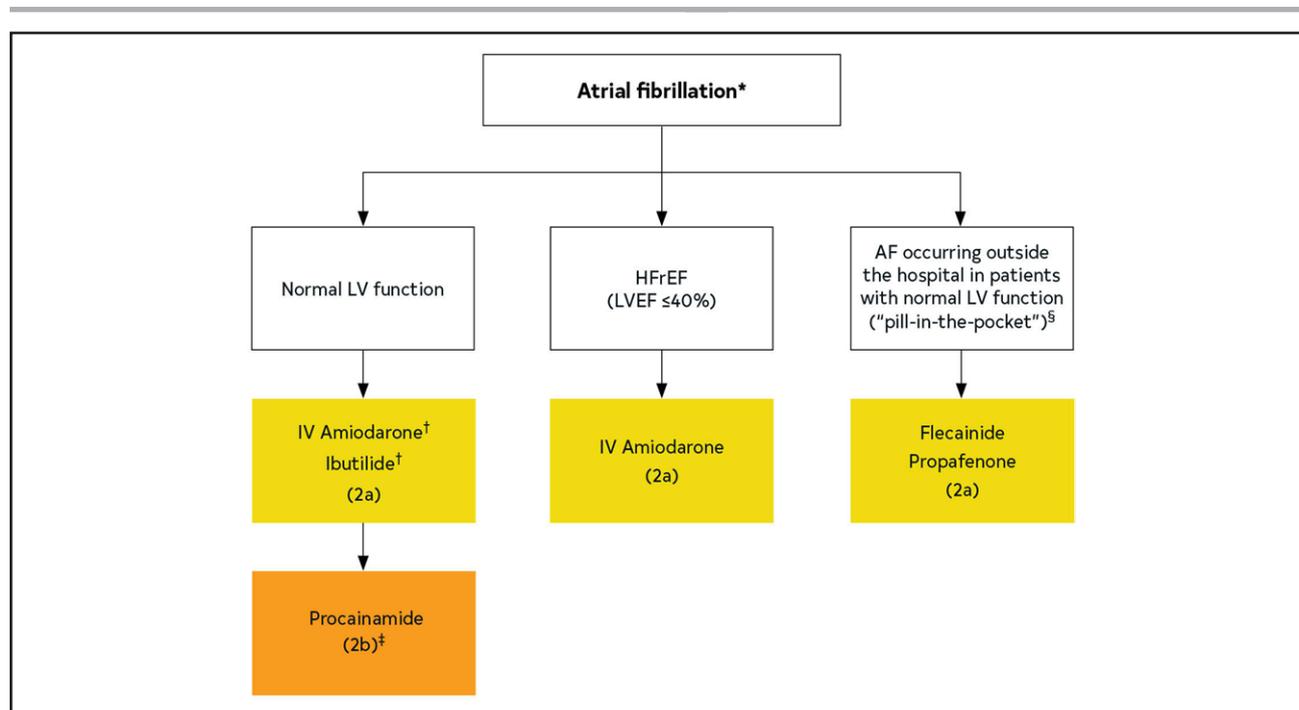
AV indicates atrioventricular; AF, atrial fibrillation; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; N/A, not applicable; NAPA, N-acetylprocainamide; TdP, torsades de pointes; and VT, ventricular tachycardia.

cardioversion,<sup>4-8</sup> although intravenous amiodarone requires a longer time for AF conversion than ibutilide. Evidence from randomized studies support the efficacy of flecainide<sup>9-11</sup> and propafenone<sup>10-14</sup> for pharmacological cardioversion, and these drugs are reasonable for administration via the PITP approach for AF occurring outside of the hospital.<sup>16-18</sup> Intravenous procainamide is more effective than placebo for pharmacological conversion of AF<sup>19</sup> but is less effective than ibutilide.<sup>22,23</sup> Dofetilide,<sup>24,25</sup> oral amiodarone,<sup>26-28</sup> and oral sotalol<sup>27,28</sup> have been shown to be effective for conversion of AF to sinus

rhythm but require several days for efficacy and therefore are not practical choices for acute pharmacological cardioversion. Data do not support intravenous sotalol for pharmacological cardioversion of AF.<sup>29,30</sup>

### Recommendation-Specific Supportive Text

1. No studies compare the efficacy of electrical cardioversion with that of pharmacological cardioversion in patients with AF who are hemodynamically unstable. However, in a retrospective, propensity score-matched analysis of 374 hemodynamically



**Figure 22. Treatment Algorithm for Pharmacological Conversion of AF to Sinus Rhythm.**

\*In the absence of preexcitation. †First dose administered in a facility that can provide continuous electrocardiographic monitoring and cardiac resuscitation because of the potential for proarrhythmia or postconversion bradycardia. ‡IV amiodarone requires several hours for efficacy; ibutilide is generally effective in 30 to 90 min but carries a higher risk of QT interval prolongation and torsades de pointes. §Recommend avoidance of IV procainamide for patients initially treated with amiodarone or ibutilide to avoid excessive QT interval prolongation and torsades de pointes. Rather, procainamide may be considered for patients for whom amiodarone and ibutilide are not considered optimal as first-line drugs. Colors correspond to Table 2. AF indicates atrial fibrillation; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LV, left ventricular; LVEF, left ventricular ejection fraction.

stable patients with AF who presented to an emergency department, the incidence of successful cardioversion was higher in the direct current cardioversion group (78.2%) than in those who underwent pharmacological conversion (59.2%) or those for whom a “wait-and-watch” approach (37.9%) was used ( $P<0.001$ ).<sup>1</sup> Compared with the “wait-and-watch” strategy, the ORs for conversion to sinus rhythm for direct current cardioversion and pharmacological cardioversion were 6.00 (95% CI, 3.38-10.66) and 2.47 (1.45-4.20), respectively ( $P<0.001$ ). Due to the potential greater efficacy of direct current cardioversion compared with that of pharmacological cardioversion, and due to the need for rapid successful conversion to sinus rhythm, immediate electrical cardioversion is generally the favored option, yet some patients may not be candidates (eg, cannot undergo anesthesia), for whom pharmacological options are available.<sup>31</sup>

2. Randomized, double-blind placebo-controlled studies have established the efficacy of ibutilide<sup>2,3</sup> for conversion of AF to sinus rhythm, with AF conversion rates of about 30% (compared with 2% in placebo groups).<sup>2,3</sup> The efficacy of ibutilide is greater for AFL (conversion rates, 38%-63%) than for AF.<sup>2,3</sup> Ibutilide terminates AF rapidly, with most

patients converting to sinus rhythm within 30 to 90 minutes (Table 22). Ibutilide is associated with a risk of QT interval prolongation and torsades de pointes. The incidence of torsades de pointes associated with ibutilide is higher in patients with reduced LVEF than in those with normal LVEF,<sup>2,3</sup> and the risk seems particularly high in patients with severely depressed LVEF.<sup>20</sup> HFrEF is an independent risk factor for ibutilide-associated torsades de pointes.<sup>3,21</sup> Therefore, ibutilide is best avoided in patients with LVEF  $\leq 40\%$ . Of note, studies have shown that a magnesium infusion immediately before administration of ibutilide may mitigate the risk of torsades de pointes and excessive QT prolongation.<sup>32,33</sup>

3. Multiple randomized studies have found intravenous amiodarone to be effective for conversion of AF to sinus rhythm.<sup>4-7</sup> A meta-analysis of randomized, placebo-controlled studies reported relative risks of sinus rhythm associated with intravenous amiodarone at 6 to 8 hours and at 24 hours of 1.23 ( $P=0.022$ ) and 1.44 ( $P<0.001$ ), respectively.<sup>8</sup> However, pharmacological cardioversion of AF with intravenous amiodarone requires 8 to 12 hours, compared with a much shorter response time with ibutilide (Table 22).

4. Single oral doses of flecainide<sup>9-11</sup> and propafenone<sup>10-14</sup> are effective for conversion of AF to sinus rhythm, with 3- to 4-hour conversion rates of 58% to 68% for flecainide (compared with 18%-29% for placebo) and 45% to 57% for propafenone (compared with 17%-29% for placebo) (Table 22). A beta blocker or nondihydropyridine calcium channel blocker is generally administered at least 30 minutes before a dose of flecainide or propafenone to prevent 1:1 atrioventricular conduction during AFL.<sup>15</sup> The PITP strategy was studied in 268 patients with stable AF of recent onset who presented to the emergency department.<sup>16</sup> Patients received single-dose oral flecainide or propafenone, and those who were successfully treated (n=210) were discharged with a plan for the PITP approach. In the 15±5-month follow-up period, single-dose flecainide or propafenone was successful in 94% of episodes. However, the incidence of adverse effects is not insignificant (6%-17%).<sup>16-18</sup> In view of this, and because in most studies, most patients received the first dose in the hospital before taking it as an outpatient, the PITP strategy should only be used for highly selected patients and after it first has been observed to be safe and effective in an inpatient setting.<sup>17,18,34</sup>
5. Intravenous procainamide was shown to be more effective than placebo for conversion of AF to sinus rhythm (conversion rates at 1 hour, 69% versus 38%; *P*=0.012) in a randomized, double-blind study of 114 patients.<sup>19</sup> However, intravenous procainamide is less effective than ibutilide for conversion of AF to sinus rhythm (conversion rates, 14% versus 76%; *P*=0.001).<sup>22</sup> The efficacy of procainamide for conversion of AF to sinus rhythm was similarly inferior to that of ibutilide in an analysis of pooled data.<sup>23</sup> In addition, intravenous procainamide is associated with a relatively high incidence of clinically significant hypotension (5%-12%)<sup>19,23</sup> and can exacerbate HFrEF.

### 8.3. Antiarrhythmic Drugs for Maintenance of Sinus Rhythm

#### 8.3.1. Specific Drug Therapy for Long-Term Maintenance of Sinus Rhythm

Recommendations for Specific Drug Therapy for Long-Term Maintenance of Sinus Rhythm		
Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
2a	A*	1. For patients with AF and HFrEF (≤40%), therapy with dofetilide <sup>†1</sup> or amiodarone <sup>†2</sup> is reasonable for long-term maintenance of sinus rhythm.
	B-NR†	

Recommendations for Specific Drug Therapy for Long-Term Maintenance of Sinus Rhythm (Continued)		
COR	LOE	Recommendations
2a	A	2. For patients with AF and no previous MI, or known or suspected significant structural heart disease, or ventricular scar or fibrosis, use of flecainide <sup>3-5</sup> or propafenone <sup>5-12</sup> is reasonable for long-term maintenance of sinus rhythm.
2a	A	3. For patients with AF without recent decompensated HF or severe LV dysfunction, use of dronedarone <sup>5,13-15</sup> is reasonable for long-term maintenance of sinus rhythm.
2a	A	4. For patients with AF without significant baseline QT interval prolongation or uncorrected hypokalemia or hypomagnesemia, use of dofetilide <sup>1,5,16 5-7,10,17,18</sup> is reasonable for long-term maintenance of sinus rhythm, with proper dose selection based on kidney function and close monitoring of the QT interval, serum potassium and magnesium concentrations, and kidney function.
2a	A	5. For patients with AF and normal LV function, use of low-dose amiodarone (100-200 mg/d) is reasonable for long-term maintenance of sinus rhythm <sup>2,5,17-22</sup> but, in view of its adverse effect profile, <sup>5,23,24</sup> should be reserved for patients in whom other rhythm control strategies are ineffective, not preferred, or contraindicated.
2b	A	6. For patients with AF without significant baseline QT interval prolongation, hypokalemia, hypomagnesemia, or bradycardia, use of sotalol <sup>5-7,10,17,18</sup> may be considered for long-term maintenance of sinus rhythm, with proper dose selection based on kidney function and close monitoring of the QT interval, heart rate, serum potassium and magnesium concentrations, and kidney function.
3: Harm	B-R	7. In patients with previous MI and/or significant structural heart disease, including HFrEF (LVEF ≤40%), flecainide and propafenone <sup>25</sup> should not be administered due to the risk of worsening HF, potential proarrhythmia, and increased mortality. <sup>26,27</sup>
3: Harm	B-R	8. For patients with AF, dronedarone should not be administered for maintenance of sinus rhythm to those with NYHA class III and IV HF or patients who have had an episode of decompensated HF in the past 4 weeks, due to the risk of increased early mortality associated with worsening HF. <sup>28</sup>

\*A LOE applies to data on dofetilide. †B-NR LOE applies to data on amiodarone.

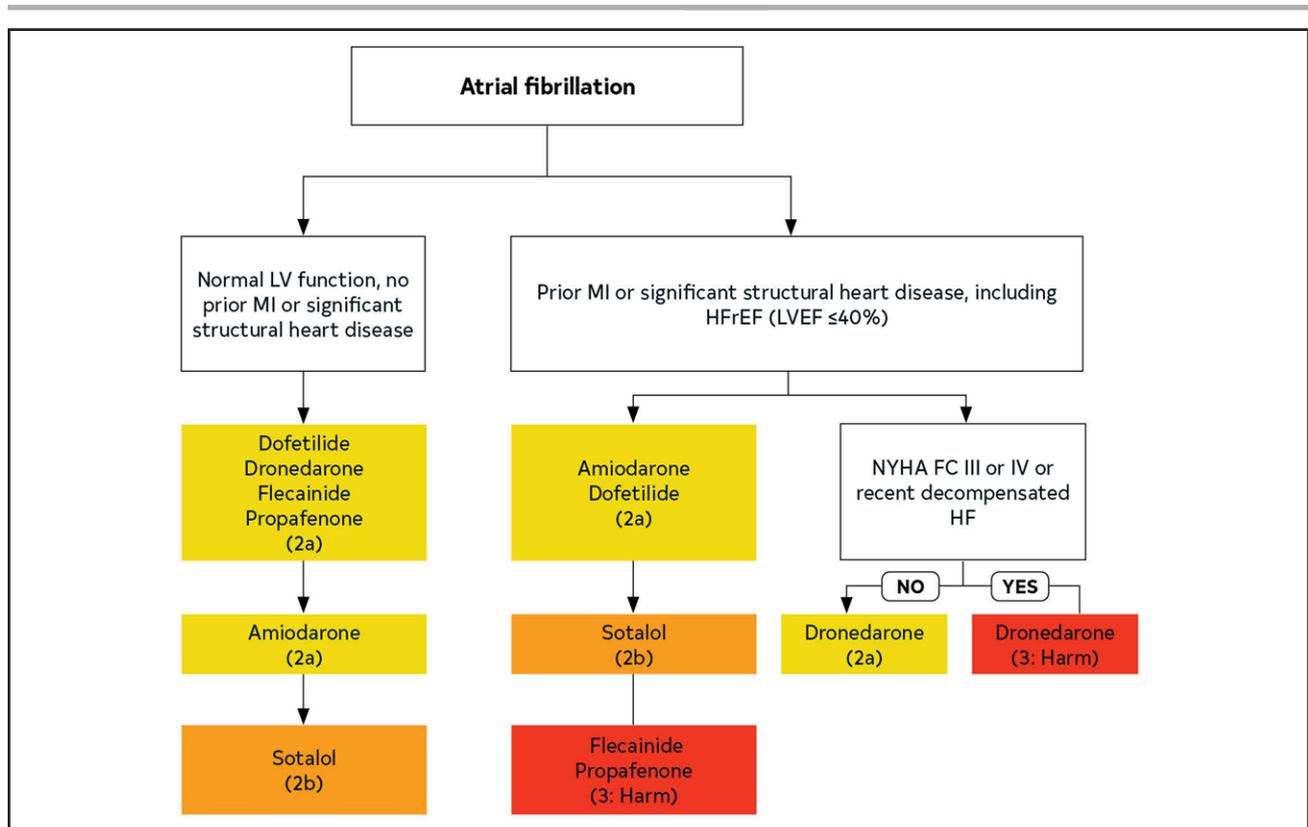
#### Synopsis

Antiarrhythmic drugs are reasonable for long-term maintenance of sinus rhythm for patients with AF who are not candidates for, or decline, catheter ablation or who prefer antiarrhythmic therapy. Flecainide<sup>3-5</sup> and propafenone<sup>5-11</sup> are options for maintenance of sinus rhythm in patients with no previous history of MI or significant structural heart disease.<sup>26,27</sup> Dronedarone is an option for maintenance of sinus rhythm in patients without recent decompensated HF or severe LV dysfunction.<sup>5,13-15</sup> Dofetilide<sup>1,5,16</sup> and sotalol<sup>5-7,10,17,18</sup> are effective for maintenance of sinus rhythm but are associated with torsades de pointes and require QT interval monitoring. Sotalol is best avoided in patients with HFrEF, because most patients are already taking a beta blocker, and the addition of sotalol is unlikely to

be well-tolerated. A Cochrane database meta-analysis of randomized studies<sup>5</sup> reported sotalol to be associated with an increase in all-cause mortality (RR, 2.23 [95% CI, 1.03-4.81]). Low-dose amiodarone is more effective than sotalol and Class IC agents for maintenance of sinus rhythm; but, in view of its adverse effects and multiple drug interactions, is best reserved for patients for whom other antiarrhythmic drugs are ineffective, not preferred, or contraindicated. However, amiodarone and dofetilide are options for maintenance of sinus rhythm for patients with HFrEF, as they are effective,<sup>1,2</sup> and most other drugs are contraindicated.

### Recommendation-Specific Supportive Text

1. In subanalyses of randomized trials, dofetilide<sup>1</sup> and amiodarone<sup>2</sup> have been shown to be effective for maintenance of sinus rhythm in patients with AF who have HF. Most antiarrhythmic agents, except amiodarone and dofetilide, are contraindicated in patients with HFrEF due to worsening of HF and/or increased mortality. Sotalol is best avoided in most patients with HFrEF, because most patients with HFrEF are already taking a beta blocker for mortality reduction, and the addition of a second beta blocker (sotalol) is unlikely to be well-tolerated. Therefore, although amiodarone is associated with a wide range of adverse effects and many clinically important drug interactions, amiodarone is often used as a first-line agent for maintenance of sinus rhythm in patients with AF and HFrEF. Dofetilide is also an option for this indication. Patients undergoing initiation or reloading of dofetilide<sup>29,30</sup> should be admitted for at least 3 days to a health care facility that can provide calculations of CrCl, continuous electrocardiographic monitoring, and availability of cardiac resuscitation.
2. Randomized, controlled studies and a comprehensive Cochrane database analysis have established the efficacy of flecainide<sup>3-5</sup> and propafenone<sup>5-11</sup> for maintenance of sinus rhythm in patients with AF. In the Flec-SL (Short-term versus long-term antiarrhythmic drug treatment after cardioversion of atrial fibrillation) trial,<sup>4</sup> flecainide prevented episodes of paroxysmal AF in 31% of patients over 4 months compared with 9% in the placebo group (0.013). Sustained-release propafenone 425, 325, and 225 mg twice daily extended the median time to the occurrence of AF, AFL, or supraventricular tachycardia (SVT) compared with placebo (>300, 291, and 112 days versus 41 days,  $P < 0.001$ , for all propafenone doses versus placebo).<sup>8</sup> Patients with previous MI or significant structural heart disease (scar or fibrosis) should not take flecainide or propafenone,<sup>26,27</sup> and individuals taking flecainide or propafenone should be concomitantly taking an atrioventricular nodal blocking agent to reduce the risk of 1:1 AFL.<sup>12</sup>
3. Randomized, controlled studies<sup>13-15</sup> and a comprehensive Cochrane database analysis<sup>5</sup> have established the efficacy of dronedarone for maintenance of sinus rhythm in patients with AF. The combined analysis (n=1237) of EURIDIS (European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm) and ADONIS (American-Australian-African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm) reported longer median times to AF recurrence in dronedarone groups versus placebo (EURIDIS: 96 versus 41 days;  $P = 0.001$ ; ADONIS 158 versus 59 days;  $P = 0.002$ ).<sup>14</sup>
4. Randomized, controlled studies and a comprehensive Cochrane database analysis<sup>5</sup> have established the efficacy of dofetilide for maintenance of sinus rhythm in patients with AF. In the SAFIRE-D (Symptomatic Atrial Fibrillation Investigative Research on Dofetilide) study,<sup>1,16</sup> the probability of remaining in sinus rhythm at 1 year was higher in patients receiving dofetilide 500 µg twice daily compared with placebo (0.58 versus 0.25;  $P < 0.001$ ). Patients undergoing initiation or reloading of dofetilide<sup>29,30</sup> should be admitted for at least 3 days to a health care facility that can provide calculations of CrCl, continuous electrocardiographic monitoring, and cardiac resuscitation.
5. Multiple randomized, controlled studies have established the efficacy of amiodarone for maintenance of sinus rhythm in AF and have shown amiodarone to be superior to other antiarrhythmic agents. In SAFE-T (Sotalol Amiodarone Atrial Fibrillation Efficacy Trial), amiodarone was superior to sotalol and placebo with respect to median time to recurrence of AF (487 versus 74 versus 6 days, respectively;  $P < 0.001$ , for amiodarone versus placebo and amiodarone versus sotalol).<sup>17</sup> In CTAF (Canadian Trial of Atrial Fibrillation), AF recurrence rates at 16 months were 35% in the amiodarone group and 63% in those randomized to combined propafenone or sotalol ( $P < 0.001$ ).<sup>19</sup> However, the adverse effects profile of amiodarone is onerous. Amiodarone is associated with a wide range of adverse effects, including pulmonary fibrosis, hypo- or hyperthyroidism, elevated transaminases, and more rarely hepatotoxicity, photosensitivity, changes in skin pigmentation, peripheral neuropathy, sinus bradycardia, QT interval prolongation and torsades de pointes, corneal microdeposits, and rarely optic neuropathy.<sup>24</sup> In addition, amiodarone is associated with many clinically relevant drug interactions.<sup>31</sup> Therefore, amiodarone is best reserved for patients who do not respond to other recommended antiarrhythmic agents or for whom other antiarrhythmic drugs are contraindicated.



**Figure 23. Treatment Algorithm for Drug Therapy for Maintenance of Sinus Rhythm.**

In each box, drugs are listed in alphabetical order. Significant structural heart disease with scar or fibrosis. Colors correspond to Table 2. HFrEF indicates heart failure with reduced ejection fraction; HF, heart failure; IV, intravenous; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and NYHA FC, New York Heart Association functional class.

6. Randomized, controlled studies and a comprehensive Cochrane database analysis<sup>5</sup> have established the efficacy of sotalol<sup>6,7,10,17,18</sup> for maintenance of sinus rhythm in patients with AF. In SAFE-T, the median time to AF recurrence was 74 days in the sotalol group, compared with 6 days for placebo ( $P < 0.001$ ).<sup>16</sup> A Cochrane database meta-analysis of 5 randomized studies totaling 1882 patients with AF<sup>5</sup> reported sotalol to be associated with an increase in all-cause mortality (RR, 2.23 [95% CI, 1.03-4.81]). However, this study included patients with advanced HF, and sotalol may still have a role in patients with preserved heart function. Patients undergoing initiation or reloading of oral sotalol should be admitted for at least 3 days to a health care facility that can provide calculations of CrCl, continuous electrocardiographic monitoring, and cardiac resuscitation. A recent FDA-approved intravenous sotalol formulation can be used to evaluate the drug safety and tolerability within 6 hours and thus may reduce cost and length of stay, although the data are limited to a small sample size and very selected population.<sup>32</sup>
7. In the randomized, double-blind, placebo-controlled CAST (Cardiac Arrhythmia Suppression Trial),<sup>26,27</sup>

the Vaughan Williams class IC antiarrhythmic agents flecainide and encainide were associated with an increased mortality rate in patients with recent MI; most patients also had LVEF  $< 50\%$ .<sup>26</sup> In the continuation of the study (CAST-II), the class IC agent moricizine also increased the mortality rate within the first 14 days of treatment.<sup>33</sup> In CASH (Cardiac Arrest Study Hamburg),<sup>34</sup> propafenone was associated with worse outcomes and increased mortality in a population of cardiac arrest survivors, most of whom had structural heart disease. Thus, IC agents are best avoided in patients with AF who have a previous MI or significant structural heart disease, including HFrEF, due to the risk of worsening HF and increased mortality.

8. ANDROMEDA (Antiarrhythmic Trial with Dronedaron in Moderate to Severe CHF Evaluating Morbidity Decrease)<sup>28</sup> was a randomized, double-blind placebo-controlled study that tested the hypothesis that dronedaron would reduce the rate of hospitalization attributable to HF and possibly reduce mortality by reducing the incidence of arrhythmic death. The study enrolled patients who were hospitalized with new or worsening HF and who had at least 1 episode of NYHA

class III or IV HF (shortness of breath on minimal exertion or at rest). More than 40% of the patients had NYHA class II HF at baseline. The investigators reported that, contrary to the study's hypothesis, the mortality rate was higher in the dronedarone group compared with that in the placebo group (8.1% versus 3.8%; HR, 2.13 [95% CI, 1.07-4.25];  $P=0.03$ ). The higher mortality rate was principally associated with worsening HF.

### 8.3.2. Inpatient Initiation of Antiarrhythmic Agents

**Recommendations for Inpatient Initiation of Antiarrhythmic Agents**  
Referenced studies that support the recommendations are summarized in the [Online Data Supplement](#).

COR	LOE	Recommendations
1	A	1. Patients with AF who are initiating, increasing the dose of, or reinitiating dofetilide therapy should be admitted for a minimum of 3 days to a facility that can provide continuous electrocardiographic monitoring, calculations of CrCl, and cardiac resuscitation, given the potential for proarrhythmia. <sup>1-7</sup>
2a	B-R	2. In patients with AF, it is reasonable to initiate sotalol therapy in a facility that can provide continuous electrocardiographic monitoring, calculations of CrCl, and cardiac resuscitation, given the potential for proarrhythmia and bradycardia. <sup>4,8-10</sup>
2a	B-NR	3. In patients with AF who are initiating PITP dosing of flecainide and propafenone with concomitant atrioventricular nodal blocking drugs, it is reasonable to receive the first dose in a facility that can provide continuous electrocardiographic monitoring, given the potential for proarrhythmia. <sup>9-13</sup>

#### Synopsis

Pharmacological rhythm control is an alternative to catheter ablation in appropriately selected patients. However, many antiarrhythmic agents have a paradoxical risk of proarrhythmia and require close monitoring on initiation. Dofetilide and sotalol confer a relatively high risk of torsades de pointes given they prolong the QT interval, and this can occur early during initiation. As such, patients need to be admitted and closely monitored when starting or reinitiating dofetilide, as well as for increasing the dosage. Many practitioners choose to initiate sotalol in an inpatient setting given it can cause torsades de pointes; furthermore, unlike dofetilide, it can also cause bradyarrhythmia. Amiodarone, flecainide, and propafenone can be started in the outpatient setting. Because PITP with class IC (with concomitant atrioventricular nodal blockers) can cause brady- or tachyarrhythmias, the first attempt during an acute episode of AF may be performed in a monitored environment if a high dose is used.

#### Recommendation-Specific Supportive Text

1. Dofetilide, a class III antiarrhythmic drug, is a selective  $I_{Kr}$  blocker that also blocks late  $Na^+$  current ( $I_{NaL}$ ) and poses a high risk for torsades de pointes. The SAFIRE-D (Symptomatic Atrial Fibrillation Investigative Research on Dofetilide) study investigated dofetilide in cardioverting and

maintaining sinus rhythm in 325 patients with AF or AFL who underwent a minimum 3-day hospitalization.<sup>1</sup> Of 241 patients randomized to dofetilide, 10 patients had QTc prolongation within the first 3 days, with 2 episodes of torsades de pointes degenerating to VF. In a substudy of the AFFIRM trial, 1 of 12 patients on dofetilide experienced torsades de pointes.<sup>3</sup> One retrospective cohort of 378 patients found no significant differences in the incidence of torsades de pointes during inpatient initiation of dofetilide and sotalol (1.3% versus 1.2%).<sup>4</sup> One systematic review found a 1% to 10% incidence of torsades de pointes in patients taking dofetilide, highest in patients with HFREF and taking higher than recommended (or not renally adjusted) doses.<sup>14</sup> In 2 randomized RCTs from the DIAMOND (Management of Hyperkalemia in Subjects Receiving Renin-angiotensin-aldosterone System Inhibitor Medications for Heart Failure with Reduced Ejection Fraction) population, in which all patients were hospitalized for at least 3 days after dofetilide was initiated, torsades de pointes occurred in 25 of 762 patients (3.3%)<sup>5</sup> and 7 of 749 patients (0.9%),<sup>7</sup> respectively, with most occurring within the first 3 days of dosing. In the DIAMOND AF substudy of these trials,<sup>6</sup> torsades de pointes occurred in 4 dofetilide-treated patients with AF (1.6%).

2. Sotalol is a class III antiarrhythmic with beta-blocking properties. Its action potential prolongation (due to the  $I_{Kr}$ -blocking properties of the d isomer in concert with  $I_{NaL}$  blockade) predisposes patients to torsades de pointes. One meta-analysis demonstrated that sotalol, compared with placebo or no treatment, was associated with a significantly higher all-cause mortality rate (RR, 2.23; 1882 patients in 5 RCTs) and proarrhythmia (RR, 3.55; 2989 patients in 12 RCTs).<sup>18</sup> The SAFE-T trial randomized 665 patients to amiodarone, sotalol, or placebo, all initiated in the outpatient setting (sotalol at 80 mg twice daily for the first week and 160 mg twice daily subsequently).<sup>15</sup> Fifteen deaths occurred in the sotalol group, 8 of which were sudden, with a nonsignificant mortality ratio of 1.8 compared with placebo. In 1 retrospective cohort of 120 patients undergoing sotalol initiation as an inpatient, 2 of 7 had torsades de pointes; 20 patients developed significant bradyarrhythmias necessitating dose reductions, and 3 patients required permanent pacing.<sup>8</sup> Intravenous sotalol was introduced in the United States in 2015 and reaches therapeutic levels rapidly and with easier dose titration to QTc levels and clinical response. As such, it may be an option for more expedient inpatient initiation (obviating the need for a 3-day initiation period).<sup>16</sup>

**Table 23. Specific Drug Therapy for Maintenance of Sinus Rhythm in Patients With AF**

Drug	Loading Dose	Maintenance Dose	Primary Route(s) of Elimination	Elimination Half-Life	Mechanism of Action	Major Adverse Effects	Important Pharmacokinetic Drug Interactions
Amiodarone	Total loading dose 6-10 g, given 400-800 mg daily in 2-4 divided doses for 1-4 wk	200 mg once daily	Liver metabolism Biliary excretion	14-59 d	Inhibits $I_{Kr}$ , $I_{Ks}$ , $I_{Na}$ , $I_{Kur}$ , $I_{to}$ , $I_{Ca-L}$ , $I_{KAch}$ Noncompetitive beta blocker	AV block Bradycardia Corneal microdeposits Elevation in transaminases Hepatotoxicity Hyperthyroidism Hypothyroidism Nausea QT prolongation Peripheral neuropathy Photosensitivity Pulmonary fibrosis Skin pigmentation (blue-gray) TdP	Moderate* inhibitor of CYP2C9, weak† inhibitor of CYP2D6 Some inhibition of CYP3A Increases plasma concentrations of warfarin, lovastatin,‡ simvastatin,§ cyclosporine Inhibits p-gp Increases plasma concentrations of digoxin
Dofetilide	N/A	CrCl >60 mL/min: 500 µg twice daily CrCl 40-60 mL/min: 250 µg twice daily CrCl 20-40 mL/min: 125 µg twice daily CrCl <20 mL/min: Contraindicated	Kidney	10 h	Inhibits $I_{Kr}$ and augments late $I_{Na}$	QT prolongation TdP	Dofetilide is renally excreted via the renal cation transport system. These drugs inhibit renal cation transport, increase plasma dofetilide concentrations, and are contraindicated in patients taking dofetilide: Cimetidine Dolutegravir Ketoconazole Megestrol Prochlorperazine Trimethoprim (alone or in combination with sulfamethoxazole) Verapamil In addition, hydrochlorothiazide (alone or in combination with triamterene) increases plasma dofetilide concentrations and should not be co-administered with dofetilide
Dronedarone	N/A	400 mg twice daily	Liver metabolism	13-19 h	Inhibits $I_{Kr}$ , $I_{Ks}$ , $I_{Na}$ , $I_{Kur}$ , $I_{to}$ , $I_{Ca-L}$ , $I_{KAch}$ . Noncompetitive beta blocker	Abdominal pain Asthenia Bradycardia Diarrhea Nausea and vomiting QT prolongation Rash TdP	Dronedarone is a substrate for CYP3A and is a moderate inhibitor of CYP3A and CYP2D6 Dronedarone is also a substrate for, and inhibitor of, p-gp Dronedarone may increase plasma concentrations of: Dabigatran Digoxin Simvastatin‡ Sirolimus Tacrolimus Warfarin These drugs may increase plasma dronedarone concentrations: Grapefruit juice These drugs may decrease plasma dronedarone concentrations: CYP3A inducers including St. John's wort, rifampin, and phenytoin

(Continued)

**Table 23. Continued**

Drug	Loading Dose	Maintenance Dose	Primary Route(s) of Elimination	Elimination Half-Life	Mechanism of Action	Major Adverse Effects	Important Pharmacokinetic Drug Interactions
Flecainide	N/A	50-300 mg/d PO divided q 8-12 h	Liver (70%) Kidney (30%) <sup>†‡</sup>	12-27 h	Inhibits I <sub>Na</sub>	Atrial flutter AV block Dizziness Dyspnea Exacerbation of HFrEF Headache Nausea QT prolongation VT Visual disturbances	Flecainide is a substrate for CYP2D6 These drugs may increase plasma flecainide concentrations: Amiodarone Duloxetine Fluoxetine Paroxetine
Propafenone	N/A	150-300 mg PO q 8 h, ER 225-425 PO q 12 h	Liver	9 h	Inhibits I <sub>Na</sub>	Atrial flutter Bradycardia AV block Dizziness Dyspnea Exacerbation of HFrEF Nausea Taste disturbances VT Visual disturbances	Propafenone is a substrate for CYP2D6 These drugs may increase plasma propafenone concentrations: Fluoxetine Paroxetine Propafenone may increase plasma digoxin concentrations Propafenone may increase plasma warfarin concentrations
Sotalol	CrCl >60 mL/min: 40-80 mg twice daily for 3 d CrCl: 40-60 mL/min: 80 mg once daily for 3 d CrCl <40 mL/min: Contraindicated	CrCl >60 mL/min: 80-160 mg twice daily CrCl: 40-60 mL/min: 80-160 mg once daily CrCl <40 mL/min: Contraindicated	Kidney	12 h	Inhibits I <sub>Kr</sub> Beta blocker d-Sotalol augments late I <sub>Na</sub>	AV block Bradycardia Bronchospasm Diarrhea Exacerbation of HFrEF Fatigue Nausea and vomiting QT prolongation TdP	None

\*Moderate inhibitor: Causes a 2-fold to <5-fold increase in AUC or a 50% to 80% decrease in clearance.

†Mild inhibitor: Causes a ≥1.25-fold but <2-fold increase in AUC or a 20% to 50% decrease in clearance.

‡Lovastatin doses should not exceed 40 mg daily in patients taking amiodarone.

§Simvastatin doses should not exceed 20 mg daily in patients taking amiodarone.

¶Simvastatin doses should not exceed 10 mg daily in patients taking dronedarone.

††Percentage of a dose excreted unchanged in urine.

AF indicates atrial fibrillation; AUC, area under the plasma concentration versus time curve; AV, atrioventricular; CrCl, creatinine clearance; CYP, cytochrome P-450; ER, extended release; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; N/A, not applicable; NAPA, N-acetylprocainamide; p-gp, p-glycoprotein; PO, orally; TdP, torsades de pointes; and VT, ventricular tachycardia.

3. The PITP strategy—a high dose of a class IC agent (flecainide 200-300 mg or propafenone 450-600 mg, with an atrioventricular nodal blocker)—can be considered for patients who experience infrequent episodes of symptomatic AF and do not prefer chronic antiarrhythmic therapy. Class IC agents are generally administered with concomitantly atrioventricular nodal blocking agents to mitigate risk of rapidly conducting AFL. Because of the risk of adverse effects and proarrhythmia with high-dose IC agents, inpatient initiation of PITP has been studied. In 1 trial evaluating the safety of outpatient PITP therapy after initiation as an inpatient, 58 of 268 (22%) patients experienced transient hypotension, 1:1 and 2:1 AFL, and symptomatic bradycardia.<sup>9</sup> In a prospective study of 43 patients who presented to the emergency department for initiation of PITP,<sup>10</sup> sinus

rhythm was restored in 30 patients; 13 patients remained in AF, and/or had symptomatic hypotension, converted to rapid AFL requiring cardioversion, or experienced a syncopal conversion pause. In a retrospective cohort<sup>13</sup> study of 273 patients initiating PITP (62% inpatient), 7 patients experienced significant adverse events, including syncope, symptomatic bradycardia/hypotension, and organization to 1:1 AFL—2 of 7 of these patients initiated PITP as an inpatient, and 2 patients required permanent pacemakers for bradycardia.

### 8.3.3. Antiarrhythmic Drug Follow-Up

Antiarrhythmic drugs are associated with important adverse effects, and monitoring is recommended to assess their efficacy for maintaining sinus rhythm and for prevention and/or early detection of adverse events.

## Amiodarone

Recommendations for follow-up monitoring for patients taking oral amiodarone are provided in Table 24. Amiodarone contains 37% iodine by weight and is therefore associated with thyroid abnormalities in 2% to 24% of patients.<sup>1</sup> In 1 study, the median time to onset of amiodarone-induced hypothyroidism was 183 days, with a median onset of hyperthyroidism of 720 days.<sup>2</sup> Oral amiodarone may also provoke elevations in hepatic transaminases and, rarely, hepatotoxicity.<sup>3</sup>

Amiodarone may cause pulmonary toxicity, most commonly in the form of interstitial lung disease or hypersensitivity syndrome,<sup>4</sup> in 1% to 2% of patients and is fatal in approximately 10% of cases. Consequently, a chest x-ray is recommended at baseline and when there is a clinical suspicion for pulmonary toxicity.<sup>4,5</sup> Pulmonary function testing, including diffusing capacity for carbon monoxide, can reveal relatively early changes in pulmonary function that may be attributable to amiodarone-associated pulmonary toxicity; however, the sensitivity of the test for routine screening of drug-induced lung toxicity in general is uncertain.<sup>4-7</sup>

In patients who develop unexplained cough and dyspnea while taking amiodarone, a chest CT scan can be helpful for diagnosis.<sup>5</sup>

Corneal microdeposits (epithelial keratopathy) are common, but visual abnormalities and light sensitivity are rare.<sup>8</sup> Therefore, an ophthalmologic examination is reasonable only if visual abnormalities develop. Amiodarone has also been associated with neurological toxicity, particularly peripheral neuropathy.

Although less common than class III antiarrhythmic agents, oral amiodarone may cause torsades de pointes<sup>9</sup>; 1 analysis estimated the incidence to be 0.7%.<sup>10</sup>

## Other Antiarrhythmic Drugs

Recommendations for follow-up of other antiarrhythmic agents used for management of AF are provided in Table 25.

## Dofetilide

Dofetilide is a potent inhibitor of  $I_{Kr}$ , augments  $I_{Na-L}$ , and is associated with torsades de pointes.<sup>9</sup> The incidence of torsades de pointes associated with dofetilide ranges from 0.9% to 3.3%.<sup>11,12</sup> However, the incidence can be substantially higher if the dofetilide dose is not properly adjusted for kidney function. Patients undergoing initiation or re-loading of dofetilide are generally admitted for at least 3 days to a health care facility that can provide calculations of CrCl, continuous electrocardiographic monitoring, and cardiac resuscitation. After discharge on a stable dose of these drugs, a 12-lead ECG, and levels for serum magnesium, potassium, and creatinine are recommended every 3 to 6 months for assessment of QTc interval duration, electrolyte balance, and renal function, and more frequently for patients concomitantly taking other QT interval-prolonging drugs or with changing kidney function, to minimize the risk of drug-associated torsades de pointes.

## Dronedarone

Rare cases of severe liver injury have been reported in association with dronedarone. These cases have occurred 4.5 to 6 months after initiation of dronedarone therapy, although 1 case of hepatotoxicity was reported as early as 2 days after initiation of dronedarone (and was ultimately fatal a few days later),<sup>13</sup> although a severe case of dronedarone-associated toxic hepatitis occurred 9 months after initiation of therapy.<sup>14</sup>

## Ibutilide

Ibutilide may prolong the QT interval and cause torsades de pointes<sup>15-22</sup> and therefore continuous electrocardiographic monitoring is recommended during infusion and for 4 hours after completion of ibutilide infusion. Ibutilide is associated with nonsustained ventricular tachycardia (VT), QT interval prolongation, and torsades de pointes. The incidence of nonsustained VT has been reported to be as high as 8.3%.<sup>23</sup> Torsades de pointes occurs in approximately 2% to 7% of patients,<sup>15-22</sup> but the

**Table 24. Recommended Monitoring for Patients Taking Oral Amiodarone**

Adverse Effect	Baseline Testing	Initial Follow-Up Testing	Additional Follow-Up Testing
Hypo- or hyperthyroidism	TSH (T4 and T3 if TSH abnormal)	3-6 mo	Every 6 mo
Hepatotoxicity	AST, ALT	3-6 mo	Every 6 mo
QT interval prolongation	ECG	Annually	–
Interstitial lung disease	Chest x-ray: Recommended CT chest: Not recommended	Chest x-ray: Unexplained cough or dyspnea or other signs/symptoms suspicious for interstitial lung disease	CT chest: As indicated to follow-up ongoing symptoms or chest x-ray findings
Corneal microdeposits (epithelial keratopathy)	Not recommended	Development of visual abnormalities, which may indicate optic neuropathy	–
Dermatologic (blue-gray skin discoloration), photosensitivity	Not recommended	Physical examination annually	Development of skin discoloration, severe sunburn
Neurological	Not recommended	Physical examination annually	Development of peripheral neuropathy or other neurological abnormalities

ALT indicates alanine transaminase; AST, aspartate transaminase; CT, computed tomography; ECG, electrocardiogram; TSH, thyroid-stimulating hormone; and TdP, torsades de pointes.

**Table 25. Recommended Monitoring for Patients Taking Other Antiarrhythmic Drugs**

Drug	Baseline Testing	Follow-Up Testing	Additional Follow-Up Testing
Dofetilide	12-lead ECG* Continuous electrocardiographic monitoring during 3-d hospitalization for dofetilide initiation Serum potassium and magnesium concentration Serum creatinine for estimation of CrCl	<b>In 3-6 mo:</b> 12-lead ECG* Serum potassium and magnesium concentration Serum creatinine for estimation of CrCl	<b>Every 3-6 mo (more frequently for patients concomitantly taking other QT interval-prolonging drugs or with changing kidney function:</b> 12-lead ECG* Serum potassium and magnesium concentration Serum creatinine for estimation of CrCl
Dronedarone	12-lead ECG* AST† ALT†	<b>Within first 6 mo:</b> AST† ALT†	–
Ibutilide	12-lead ECG* Determination of serum potassium and magnesium concentrations and correction of hypokalemia and/or hypomagnesemia is recommended before initiation of the infusion	Continuous electrocardiographic monitoring for assessment of QTc interval duration is recommended for at least 4 h after infusion or until the QTc has returned to baseline to minimize the risk of ibutilide-associated TdP	–
Procainamide	12-lead ECG* BP	Electrocardiographic monitoring for assessment of rhythm, QRS width and QTc interval is recommended during the infusion to minimize the risk of procainamide-associated ventricular proarrhythmia, including TdP BP monitoring is recommended during the infusion to detect clinically relevant hypotension	–
Sotalol	12-lead ECG* Continuous electrocardiographic monitoring during 3-d hospitalization for sotalol initiation Serum potassium and magnesium concentration Serum creatinine for estimation of CrCl	<b>In 3-6 mo:</b> 12-lead ECG* Serum potassium and magnesium concentration Serum creatinine for estimation of CrCl	<b>Every 3-6 mo (more frequently for patients concomitantly taking other QT interval-prolonging drugs or with changing kidney function:</b> 12-lead ECG* Serum potassium and magnesium concentration Serum creatinine for estimation of CrCl

\*Assess rhythm and calculate QTc.

†To facilitate early detection of potential dronedarone-associated hepatotoxicity.

ALT indicates alanine transaminase; AST, aspartate transaminase; BP, blood pressure; ECG, electrocardiogram; CrCl, creatinine clearance; and TdP, torsades de pointes.

incidence increases substantially in patients with depressed LVEF.<sup>22</sup> Most reported cases of ibutilide-associated nonsustained VT and torsades de pointes have occurred within 30 minutes after the last dose; torsades de pointes has rarely been reported as late as 2.5 hours after an ibutilide infusion.<sup>22</sup> QTc intervals generally return to baseline within 2 to 3 hours after a dose.

The risk of drug-induced torsades de pointes is higher in patients with hypokalemia and/or hypomagnesemia. Hypokalemia has been reported to be present in 17% to 70% of patients who have developed drug-induced torsades de pointes.<sup>24–27</sup> Similarly, hypomagnesemia has been reported to be a contributing factor to numerous published cases of drug-induced torsades de pointes.<sup>27–29</sup> Therefore, maintenance of serum potassium and magnesium concentrations within the normal range is important before administration of ibutilide, and magnesium supplementation may mitigate the risk of torsades de pointes.

### Procainamide

Intravenous procainamide is associated with hypotension in 5% to 12% of patients when used for management of AF,<sup>30,31</sup> and BP monitoring is recommended. Intravenous procainamide is also associated with widening of the

QRS complex and prolongation of the QT interval and may provoke proarrhythmia in the form of monomorphic VT<sup>32</sup> and torsades de pointes.<sup>33</sup>

### Sotalol

Sotalol is a potent inhibitor of  $I_{Kr}$ , augments  $I_{Na-L}$ , and is associated with torsades de pointes, with an incidence ranging from 0.4% to 2.3%.<sup>34,35</sup> Patients undergoing initiation or dose escalation of sotalol are often admitted for at least 3 days to a health care facility that can provide calculations of CrCl, continuous electrocardiographic monitoring, and cardiac resuscitation. A new intravenous form of sotalol was recently FDA approved, which may obviate the need for 3-day admission. After discharge on a stable dose of these drugs, a 12-lead ECG, and levels of serum magnesium, potassium, and creatinine are recommended every 3 to 6 months for assessment of QTc interval duration, electrolyte balance, and renal function, and more frequently for patients concomitantly taking other QT interval-prolonging drugs or with changing kidney function, to minimize the risk of drug-associated torsades de pointes.

### 8.3.4. Upstream Therapy

Pharmacological treatments targeting upstream pathways have included glucocorticoids, ACE inhibitors,

ARBs, aldosterone antagonists, statins, omega-3 polyunsaturated fatty acids, antioxidants, and sodium-glucose cotransporter 2 inhibitors (see **Section 5, “Lifestyle and Risk Factor Modification for AF Management”**). Targeting inflammation, a randomized study of glucocorticoids reduced recurrent AF after first occurrence of persistent AF, but adverse effects inhibit long-term steroid use.<sup>1-9</sup> Statins reduced postoperative AF in small RCTs.<sup>10-14</sup> However, an adequately powered placebo-controlled trial of rosuvastatin did not reduce postoperative AF.<sup>15</sup> Statins do not prevent AF in other cardiovascular settings.<sup>16</sup> RCTs and a meta-analysis provide limited though consistent support for the antioxidant ascorbic acid for postoperative AF.<sup>17</sup> Targeting fibrosis, small or secondary studies of RCTs reported lower new AF with ACE inhibitors or ARBs.<sup>2-9</sup> However, larger RCTs targeting AF failed to reduce recurrent AF.<sup>18-20</sup> RCTs showed that MRAs reduced new-onset atrial arrhythmias in patients with HFrEF along with improvement of other cardiovascular outcomes.<sup>21,22</sup> In patients with type 2 diabetes, HF, or CKD, sodium-glucose cotransporter 2 inhibitors appear to prevent new AF.<sup>23-25</sup> In contrast, omega-3 fatty acids do not appear to reduce AF and, in 1 large study, was associated with higher occurrence of AF.<sup>26-31</sup> With only limited or inconsistent data, no recommendations are made for use of these upstream therapies for prevention of AF.

**8.4. AF Catheter Ablation**

Recommendations for AF Catheter Ablation		
Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	A	1. In patients with symptomatic AF in whom antiarrhythmic drugs have been ineffective, contraindicated, not tolerated or not preferred, and continued rhythm control is desired, catheter ablation is useful to improve symptoms. <sup>1-10</sup>
1	A	2. In selected patients (generally younger with few comorbidities) with symptomatic paroxysmal AF in whom rhythm control is desired, catheter ablation is useful as first-line therapy to improve symptoms and reduce progression to persistent AF. <sup>11-16</sup>
1	A	3. In patients with symptomatic or clinically significant AFL, catheter ablation is useful for improving symptoms. <sup>17-19</sup>
2a	B-NR	4. In patients who are undergoing ablation for AF, ablation of additional clinically significant supraventricular arrhythmias can be useful to reduce the likelihood of future arrhythmia. <sup>17,18,20-27</sup>
2a	B-R	5. In patients (other than younger with few comorbidities) with symptomatic paroxysmal or persistent AF who are being managed with a rhythm-control strategy, catheter ablation as first-line therapy can be useful to improve symptoms. <sup>11-13,28</sup>

Recommendations for AF Catheter Ablation (Continued)		
COR	LOE	Recommendations
Cost Value Statement: Intermediate	B-R	6. Catheter ablation for symptomatic AF provides intermediate economic value compared with antiarrhythmic drug therapy. <sup>29,30</sup>
2b	B-NR	7. In selected* patients with asymptomatic or minimally symptomatic AF, catheter ablation may be useful for reducing progression of AF and its associated complications. <sup>31-39</sup>

\*Younger patients with few comorbidities and a moderate to high burden of AF or persistent AF and AFL.

**Synopsis**

Catheter ablation has become an established therapy for AF because of multiple RCTs and evidence from large registries and continues to evolve as new technologies are developed. Previous professional society documents have provided different recommendations for catheter ablation dependent on whether AF was persistent or paroxysmal.<sup>25,40</sup> More recent information has shown that ablation for AF is more effective than antiarrhythmic drugs for both persistent and paroxysmal AF and that earlier implementation of rhythm control strategies is an important factor for improving AF ablation success rates.<sup>4,35,41-44</sup> As with all strategies for rhythm control of AF, impact on a patient’s goals of care and QOL should be the focus. For example, significantly reducing the frequency and duration of AF episodes but not eliminating all future episodes of AF may represent a clinically important improvement. Although RCTs have mainly used younger patients (<70 years of age) who also experience the largest benefits, observational studies have reported improvement in QOL with catheter ablation in older patients.<sup>3-6,8,45-47</sup>

**Recommendation-Specific Supportive Text**

1. In patients who have not responded to an antiarrhythmic drug due to a high burden of recurrent AF or adverse effects from the medication, RCTs have consistently demonstrated lower risk for recurrent symptomatic AF after ablation when compared with using another antiarrhythmic medication.<sup>1-10</sup> As an example, in STOP-AF, patients who had failed ≥1 antiarrhythmic drug (approximately 70% and 30% for 1 or 2 failed drugs, respectively) were randomized to either another antiarrhythmic drug or catheter ablation. At 1 year follow-up, catheter ablation was associated with a treatment success rate of 70% compared with 7% in the drug arm.<sup>10</sup> Similarly, in the Thermo-cool (NAVISTAR THERMOCOOL Catheter for the Radiofrequency Ablation of Symptomatic Paroxysmal Atrial Fibrillation) trial, patients with paroxysmal AF who had failed 1 antiarrhythmic medication were randomized to catheter ablation or another antiarrhythmic drug. After 9 months, 66% of patients in the catheter ablation

- group were free from recurrent arrhythmia compared with 16% in the antiarrhythmic drug group.<sup>8</sup> Finally, most recently, in the CABANA trial, 80% of patients were on an antiarrhythmic medication and thought to be candidates for AF ablation and were randomized to catheter ablation or continued antiarrhythmic therapy. Catheter ablation was associated with a nearly 50% reduction in recurrent AF (HR, 0.52 [95% CI, 0.45-0.60];  $P < 0.001$ ).<sup>4,28</sup>
- In selected patients with paroxysmal AF, ablation is a suitable first-line option. Several initial RCTs suggested a decrease in recurrent AF or AF burden with catheter ablation when compared with antiarrhythmic drugs.<sup>16</sup> More recent trials have shown a significant reduction in recurrent AF with catheter ablation compared with antiarrhythmic drugs. In a follow-up report of 1 study, after 3-year follow-up, catheter ablation continued to be associated with a significant decrease in recurrent atrial tachyarrhythmias when compared with antiarrhythmic drugs (HR, 0.51 [95% CI, 0.38-0.67]).<sup>14</sup> More importantly, episodes of persistent AF developed in only 1.9% of patients randomized to catheter ablation compared with 7.4% of patients in the antiarrhythmic drug arm (HR, 0.25 [95% CI, 0.13-0.70]).<sup>14</sup> All of the studies that have evaluated catheter ablation as an initial strategy for rhythm control in patients with paroxysmal AF, although fairly standard exclusion criteria were used, enrolled relatively young patients (average age approximately 60 years) who had relatively few comorbidities (if present, mainly hypertension).<sup>16</sup>
  - AFL is most commonly due to the critical isthmus formed by the inferior vena cava and the tricuspid valve. More rarely, in patients who have not undergone previous ablation procedures atypical AFL or focal ATs can be observed. Catheter ablation of typical AFL is effective and relatively low risk.<sup>17-19</sup> In an older meta-analysis of AFL ablation studies, AFL ablation was associated with an acute success rate of 90% and a complication rate of 2.6%.<sup>18</sup> The occurrence of AF after AFL ablation was 34%, with a recurrence rate of 23% in those patients without a history of AF compared with 53% in patients with a history of AF. By 5 years, AF developed in 60% to 70% of patients regardless of whether the patient had a history of AF before the AFL ablation. Little evidence is available in these studies for the clinical significance of AF after AFL ablation.
  - AF can be associated with other atrial arrhythmias, particularly AFL.<sup>20-22</sup> During ablation for AF, ablation of previously documented or inducible sustained SVT or AFL is useful to reduce the likelihood of recurrent arrhythmias.<sup>22-25</sup> Although ablation alone for AF in patients with both AF and AFL will reduce the likelihood of AFL, and ablation targeting an inducible SVT in a patient with AF may reduce future AF, in both cases the likelihood of recurrent arrhythmias is high, although the actual recurrence rate will depend on the specific population.<sup>17,18,25-27,48,49</sup> Conversely, prophylactic catheter ablation of the CTI in patients without documented or inducible AFL likely has minimal benefit.<sup>50</sup> Alternatively, in 1 study, cryoballoon PVI as first-line treatment for AFL is equally effective compared with standard CTI ablation for preventing recurrence of atrial arrhythmia and better at preventing new-onset AF.<sup>51</sup>
  - Several randomized trials have compared catheter ablation to AADs as first-line therapy for AF.<sup>11-13</sup> In the MANTRA-AF study, ablation and antiarrhythmic drugs as first-line therapy for paroxysmal AF was evaluated. Although no differences in AF were identified during the first 18 months, at 24-month follow-up, ablation was associated with a lower AF burden (ablation, 9% versus antiarrhythmic drugs, 18%;  $P = 0.004$ ).<sup>11</sup> Subsequent studies have demonstrated similar results: In the EARLY-AF (Early Aggressive Invasive Intervention for Atrial Fibrillation) study, at 1-year follow-up, recurrent atrial arrhythmias were identified in 43% of the ablation group and 68% of the antiarrhythmic drug group ( $P < 0.001$ ), and in the STOP AF First (Cryoballoon Catheter Ablation in an Antiarrhythmic Drug Naive Paroxysmal Atrial Fibrillation) study, recurrent atrial arrhythmias were identified in 25% of the ablation group and 55% of the antiarrhythmic drug group ( $P < 0.001$ ).<sup>12,13</sup> Procedural complications were observed in 2% to 5% of patients in all 3 studies.<sup>11-13</sup> Although AF burden was significantly reduced with ablation compared with antiarrhythmic drug therapy in EARLY-AF, AF burden was low with either strategy (percentage of time in AF: ablation, 0.6% versus antiarrhythmic drugs, 3.9%) and, in all 3 trials, the average age was  $\leq 60$  years.<sup>11-13</sup> Although these trials enrolled patients with paroxysmal AF, recent studies have consistently found that catheter ablation is more commonly used and also effective in patients with persistent AF, particularly if of relatively recent onset ( $< 1$  year).<sup>28</sup>
  - Catheter ablation for AF is a costly procedure yet appears to provide value by improving the symptoms of AF and patient QOL. Some of the initially higher costs of the ablation procedure may be offset by reductions in subsequent cardiovascular hospitalizations. Formal economic analyses have been performed alongside 2 randomized controlled clinical trials. Both trials showed higher costs and improved QOL during follow-up, with incremental cost-effectiveness ratios of \$58 000 and €51 000

per quality adjusted life-year added, values within the intermediate value range (between \$50 000 and \$150 000 per quality<sup>29,30,52–55</sup> adjusted life-year added) by ACC/AHA criteria. Models of the cost-effectiveness of catheter ablation have reported more favorable results, but their results generally depended on assumptions that ablation reduced mortality, or ischemic stroke, or both, which have not been proven.

- In most patients, continued untreated AF will lead to progression and higher AF burden associated with worse clinical outcomes.<sup>31–39</sup> In patients with subclinical AF <24 hours, progression to overt AF or episodes >24 hours occurs at a rate of 8.8% per year, and those patients who develop AF are more likely to be hospitalized for HF.<sup>56</sup> Several observational studies have reported AF progression may be improved by using a catheter-based ablation rhythm-control strategy.<sup>33–35,37,38</sup> As an example, in 1 randomized trial that was stopped prematurely, in 255 patients with paroxysmal AF randomized to catheter ablation or antiarrhythmic medication, freedom from persistent AF or AT was significantly higher with catheter ablation (ablation: 2.4%, versus antiarrhythmic medication, 17.5%, 1-sided  $P=0.0009$ ).<sup>57</sup> However, serious adverse events associated with the ablation were observed in 8% of patients.<sup>57</sup> Despite the potential risks associated with catheter ablation, in a recent analysis of a large registry that specifically evaluated asymptomatic patients, rhythm control was associated with an improvement in the composite outcome of cardiac death, ischemic stroke, and hospitalization for HF.<sup>58</sup> The impact was largest in those patients who underwent catheter ablation for rhythm control, particularly in those with paroxysmal AF, LA diameters  $\leq 50$  mm,<sup>58</sup> or higher stroke risk (CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 3$ ). In a post hoc analysis of EAST-AFNET 4, the magnitude of benefit from a rhythm-control strategy for reducing the primary composite outcome of cardiovascular death, stroke, or hospitalizations for HF or ACS was independent of symptom status, and catheter ablation for rhythm control was used in approximately 20% of patients, whether symptomatic or not.<sup>59</sup>

#### 8.4.1. Patient Selection

Patient selection is the first step and a critically important step in deciding candidacy for catheter ablation.<sup>1–4</sup> Younger patients are likely to derive greater long-term benefit, including delaying AF progression. However, clinical trials have demonstrated improved cardiovascular outcomes with rhythm control, even with median ages in the 70s.<sup>5</sup> Patients with minimal atrial enlargement have the best outcomes,<sup>6</sup> whereas increased myocardial fibrosis<sup>7b</sup> and more persistent forms of AF are associated

with higher rates of recurrence after ablation. Time from diagnosis to ablation is also associated with improved outcomes after ablation.<sup>9,10</sup> Although the likelihood of recurrence of AF is 1 factor that should be considered, it is difficult to predict,<sup>11</sup> and certain patients may derive even greater benefits from catheter ablation, such as in patients with HFrEF, who have been shown to have improved functional status, LV function, and cardiovascular outcomes.<sup>12–14</sup>

In some patients, ablation should be avoided as it is unlikely to be successful due to overwhelming substrate or ongoing physiologic processes that either strongly perpetuate the risk of AF or make maintenance of sinus rhythm unlikely. These situations include but are not limited to advanced infiltrative cardiomyopathies like amyloid, severe mitral stenosis or regurgitation, and cor pulmonale.

#### 8.4.2. Techniques and Technologies for AF Catheter Ablation

##### Recommendations for Techniques and Technologies for AF Catheter Ablation

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

COR	LOE	Recommendations
1	A	1. In patients undergoing ablation for AF, PVI is recommended as the primary lesion set for all patients unless a different specific trigger is identified. <sup>1–7</sup>
2b	B-R	2. In patients undergoing ablation for AF, the value of other endpoints beyond PVI such as noninducibility and ablation of additional anatomic ablation targets (eg, posterior wall sites, low voltage areas, complex fractionated electrograms, rotors) is uncertain. <sup>8–18</sup>

#### Synopsis

Catheter ablation is now established as an effective option for rhythm control in patients with AF and AFL.<sup>1–7,16</sup> However, in patients with AF, additional ablation targets beyond isolation of PVI as a routine strategy have not reduced AF recurrence or burden in RCTs.<sup>8–18</sup> Although achieving durable pulmonary vein ablation in patients with AF has been associated with less recurrent arrhythmias, other endpoints, such as termination of F and noninducibility, have not been associated with improved outcomes.<sup>19–28</sup> Significant complications of AF ablation include stroke and TIAs, pericardial effusion, and vascular complications.<sup>16</sup> The most serious complication that occurs after the ablation procedure is development of an esophageal atrial fistula, although other complications, such as PV stenosis can occur.<sup>8–18</sup>

#### Recommendation-Specific Supportive Text

- Multiple randomized studies have shown that PVI is more effective than medical therapy for reducing AF burden.<sup>1–7</sup> A recent meta-analysis of 6 RCTs found that strategies that included PVI were associated with a 50% reduction in the development of recurrent AF when compared with strategies that did not include PVI.<sup>7</sup>

2. Studies have evaluated the use of different endpoints immediately after catheter ablation for predicting durable PVI and the likelihood of future arrhythmias with mixed results.<sup>19–28</sup> In the largest randomized study to date, techniques such as waiting for 30 minutes, using adenosine triphosphate to facilitate PV reconnection, or the combination of waiting and using adenosine were not superior to no testing for predicting durable pulmonary vein isolation or reduction in future arrhythmias. Although noninducibility remains important in determining whether ablation for paroxysmal SVT has been successful, noninducibility after AF ablation or termination of AF with ablation have had mixed results for predicting the likelihood of future recurrence.<sup>19–29</sup>

Multiple ablation targets beyond PVI have been evaluated in randomized controlled and observational trials, including the LAA, posterior wall, the ligament of Marshall, or atrial scar.<sup>8–18</sup> Results have been mixed, and no strategy has emerged that is broadly applicable in all patients, likely because the individual mechanisms for AF vary from patient to patient.<sup>8–18</sup> Targeting large areas of atrial tissue may have potential negative consequences, including a higher likelihood of complications such as atrioesophageal fistula, poor LA mechanics, atypical flutters, and increased risk for stroke.<sup>30–35</sup>

**8.4.3. Management of Recurrent AF After Catheter Ablation**

Recommendations for Management of Recurrent AF After Catheter Ablation		
Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	B-NR	1. In patients with recurrent symptomatic AF after catheter ablation, repeat catheter ablation or antiarrhythmic drug therapy is useful to improve symptoms and freedom from AF. <sup>1–11</sup>
2a	A	2. In some patients who have undergone catheter ablation of AF, short-term antiarrhythmic drug therapy after ablation can be useful to reduce early recurrences of atrial arrhythmia and hospitalization. <sup>12–16</sup>

**Synopsis**

Recurrences of AF are common after a first ablation procedure, occurring in 30% to 40% of patients in contemporary clinical trials.<sup>1,2</sup> In general US practice, 11% of patients undergoing de novo ablation have a repeat ablation by 1 year.<sup>3</sup> Patients often experience improved symptoms and QOL even when they experience recurrence after catheter ablation.<sup>4</sup> Nonetheless, recurrent atrial arrhythmia that leads to symptoms or LV dysfunction requires treatment.

**Recommendation-Specific Supportive Text**

1. In general, successful suppression of AF improves with additional or multiple ablation procedures.<sup>5–7</sup>

The absolute limit to the number of ablations a patient can undergo is unknown. For example, it is possible that a patient with previous PVI and repeat ablations with substrate modification may benefit from ablation of PV to LA reconnections, or ablation of additional triggers. However, repeat ablations carry increased risks of adverse effects. These risks are rare but include PV stenosis and stiff LA syndrome.<sup>8,9,17</sup>

Many of the randomized clinical trials, which have demonstrated superiority of catheter ablation over antiarrhythmic drug therapy, included repeat ablation procedures as part of their prospective study designs.<sup>1,10,11,18</sup> Randomized data also suggest that repeat ablation is superior to antiarrhythmic drug therapy for the treatment of recurrent AF after first ablation.<sup>19</sup> Although no large direct head-to-head trials are available of repeat catheter ablation versus no repeat catheter ablation, the aggregate data from randomized trials suggest that repeat ablation improves arrhythmia suppression and symptom control. Limited numbers of randomized trials can guide the optimal approach to repeat catheter ablation (beyond reisolation of the PVs).<sup>12,13</sup>

Although randomized data suggest that repeat ablation is superior to antiarrhythmic drug therapy for the treatment of recurrent AF after first ablation,<sup>19</sup> recurrences of AF after catheter ablation can also be successfully treated with antiarrhythmic drug therapy even when these same medications may have been ineffective before ablation.<sup>3,14</sup> Antiarrhythmic drugs have also been associated with decreased recurrent atrial arrhythmias in those who have undergone previous ablation.<sup>14</sup> Other studies have shown that use of previously ineffective antiarrhythmic therapy can be effective after ablation.<sup>15</sup> Optimal rhythm control often requires a combined approach of catheter ablation and adjunctive antiarrhythmic drug therapy, especially in patients with long-standing persistent AF or patients with advanced atrial myopathies.

2. Several clinical trials have demonstrated the efficacy and safety of short-term (3-6 months postablation) antiarrhythmic therapy to prevent recurrences of AF, symptoms, cardioversion, and hospitalization after ablation.<sup>16,20,21</sup> Moreover, continued use of antiarrhythmic drugs beyond the blanking period (3 months) may reduce the risk of recurrent atrial arrhythmias out to 1 year.<sup>15</sup> Meta-analysis of randomized trials evaluating the use of short-term antiarrhythmic drug therapy have determined that it significantly decreases the risk of early, but not late, recurrence.<sup>22,23</sup> Observational data from nationwide practice data also suggest that antiarrhythmic therapy after ablation can reduce hospital readmissions by 37% in the

short term (90 days) after ablation.<sup>24</sup> Although the evidence base for short-term antiarrhythmic drug therapy after ablation is robust, the decision to use short-term antiarrhythmic drug therapy should be based on the patient's risk and informed by SDM.

#### 8.4.4. Anticoagulation Therapy Before and After Catheter Ablation

Recommendations for Anticoagulation Therapy Before and After Catheter Ablation		
Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	B-NR	1. In patients on warfarin who are undergoing catheter ablation of AF, catheter ablation should be performed on uninterrupted therapeutic anticoagulation with a goal INR of 2.0 to 3.0. <sup>1</sup>
1	A	2. In patients on a DOAC who are undergoing catheter ablation of AF, catheter ablation should be performed with either continuous or minimally interrupted oral anticoagulation. <sup>2-10</sup>
1	B-NR	3. In patients who have undergone catheter ablation of AF, oral anticoagulation should be continued for at least 3 months after the procedure with a longer duration determined by underlying risk. <sup>11</sup>
1	B-NR	4. In patients who have undergone catheter ablation of AF, continuation of longer-term oral anticoagulation should be dictated according to the patients' stroke risk (eg, CHA <sub>2</sub> DS <sub>2</sub> -VASC score ≥2). <sup>11-17</sup>

#### Synopsis

Catheter ablation has been demonstrated in randomized clinical trials to reduce arrhythmia burden improve QOL and, in select populations, it has been shown to improve cardiovascular outcomes. Complications after catheter ablation are infrequent, yet the risk of thromboembolic events is increased after ablation. The risk of stroke in the first 30 days after ablation is 0.8%.<sup>18</sup> Thus, oral anticoagulation before, during, and after catheter ablation procedures is paramount.

#### Recommendation-Specific Supportive Text

1. All patients undergoing catheter ablation require intraprocedural intravenous anticoagulation with heparin or direct thrombin inhibitors in those with heparin allergies. Management of oral anticoagulation during these procedures is also critically important. In those patients undergoing catheter ablation of AF who are taking warfarin for their oral anticoagulation, evidence from observational studies and randomized trial data suggest that optimal efficacy and safety is achieved with uninterrupted warfarin. Patients undergoing catheter ablation of AF who have subtherapeutic INRs or interrupted warfarin have more evidence of silent cerebral ischemic events on brain magnetic resonance imaging after the procedure.<sup>1</sup> In the COMPARE (Role of Coumadin in Preventing Thromboembolism in Atrial Fibrillation [AF] Patients Undergoing Catheter Ablation) trial, interruption of warfarin was highly

associated with periprocedural thromboembolic events (OR, 13 [95% CI, 3.1-55.6];  $P < 0.001$ ).<sup>1</sup> Patients treated with uninterrupted warfarin had lower rates of thromboembolic events (5% versus 0.25%;  $P < 0.001$ ) and lower rates of periprocedural bleeding compared with those in whom warfarin was stopped or interrupted.

2. Although uninterrupted warfarin is superior to interrupted warfarin among persons undergoing catheter ablation of AF, meta-analyses have demonstrated lower risks of major bleeding with uninterrupted direct oral anticoagulation compared with uninterrupted vitamin K antagonism.<sup>2</sup> Many randomized trials have been completed that compare uninterrupted DOACs versus uninterrupted VKAs, including trials of apixaban,<sup>3,4</sup> dabigatran,<sup>5</sup> edoxaban,<sup>6</sup> and rivaroxaban.<sup>7</sup> In aggregate, these trials have demonstrated the noninferiority of uninterrupted direct-acting oral anticoagulation compared with uninterrupted vitamin K antagonism. Several randomized trials also compare minimally interrupted direct-acting oral anticoagulation versus uninterrupted direct-acting oral anticoagulation<sup>8</sup> or uninterrupted vitamin K antagonism.<sup>9</sup> These clinical trials and meta-analyses suggest that outcomes with minimally interrupted direct-acting oral anticoagulation are not different compared with continuous anticoagulation.<sup>10</sup>
3. The risk of thromboembolic and stroke events increases after ablation due to vascular and cardiac instrumentation, release of tissue factor, and myocardial injury. Most randomized clinical trials of catheter ablation that demonstrate a low risk of periprocedural stroke mandated oral anticoagulation for a minimum of 2 months after ablation to reduce the risk of stroke, regardless of CHA<sub>2</sub>DS<sub>2</sub>-VASC score.<sup>19</sup>
4. Greater burden or time in AF is associated with higher rates of stroke.<sup>12-14</sup> Accordingly, reducing exposure to AF via catheter ablation might be expected to reduce the risk of stroke. Although some observational studies have identified lower stroke risk after catheter ablation,<sup>15,16</sup> randomized clinical trials of catheter ablation have not demonstrated reductions in stroke.<sup>11,17</sup> Observational data regarding the risk of stroke after catheter ablation of AF are mixed and vary across study design and methods. For example, in an analysis of 4050 patients undergoing catheter ablation with a CHA<sub>2</sub>DS<sub>2</sub>-VASC score ≥2 in Denmark, the risk after ablation was low and comparable in those who did (0.93/100 patient years) and did not (0.97/100 patient years) discontinue anticoagulation >3 months after ablation.<sup>20</sup> In contrast, a study of 6866 patients who underwent catheter ablation of AF in US clinical practice found that the risk of stroke was

**Table 26. Complications After AF Catheter Ablation**

Complication	Frequency of Complication <sup>1-4</sup>	Timing of Complication	Signs and Symptoms	Diagnosis	Treatment
LA-esophageal fistula	0.2%	1-4 wk	Chest pain, pain with swallowing, fever, stroke symptoms	CT scan of chest	Surgery
Cardiac perforation with tamponade	0.4%-1.5%	During procedure	Hypotension	Echocardiography	Pericardiocentesis
CVA/TIA	0.1%-1.0%	During procedure and up to 1 wk	Neurological findings	MRI or CT scan	Anticoagulate when safe
PV stenosis	0.1%-0.8%	Months	Dyspnea, hemoptysis	MRI or CT scan	Stent
Phrenic nerve paralysis	0.2%-0.4%	During procedure	Dyspnea	Fluoroscopy	Time
Vascular access complications	1%-7%	During procedure and up to 1 mo	Pain, swelling at access site	Ultrasound or CT scan	Observation
Vascular access complications requiring surgery	0.1%-0.3%	During procedure and up to 1 mo	Pain and swelling at access site	Ultrasound or CT scan	Surgery
Death	0.1%-0.4%	During procedure			
Pneumonia	0.4%-1.0%	Days	Cough, fever	Chest x-ray	Antibiotics

AF indicates atrial fibrillation; CT, computed tomography; CVA, cerebrovascular accident; LA, left atrial; PV, pulmonary vein; TIA, transient ischemic attack; and MRI, magnetic resonance imaging.

increased in patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥2 who discontinued oral anticoagulation after 3 months (HR, 2.48 [95% CI, 1.11-5.52]; *P*<0.05).<sup>21</sup> In this same study, no increased risk was observed that was associated with discontinuation after 3 months in those with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 0 to 1. Ongoing randomized trials are investigating whether oral anticoagulation can be safely discontinued in patients who have no significant arrhythmia recurrences after catheter ablation. Finally, the OPTION (Comparison of Anticoagulation With Left Atrial Appendage Closure After AF Ablation) trial (NCT03795298) will test whether LAAO is noninferior to continued oral anticoagulation after catheter ablation of AF.<sup>22</sup> Given (1) the absence of randomized data that directly address this question, (2) the absence of consistent data demonstrating a lower risk of stroke after ablation, and (3) increased rates of stroke among persons with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥2 who discontinue oral anticoagulation after 3 months, persons who have undergone catheter ablation AF should continue guideline-directed oral anticoagulation beyond 3 months based on their stroke risk, such as those with moderate-high risk of stroke.

**8.4.5. Complications After AF Catheter Ablation**

Complications of AF catheter ablation occur in approximately 5% of patients, with most being vascular (Table 26).<sup>1-4</sup> However, several life-threatening complications may occur. Complications are more common with annual operator procedures <25 patients and hospital procedures <50 patients.<sup>1</sup> Some studies demonstrate a higher incidence of complications in wom-

en,<sup>1</sup> but the CABANA RCT did not.<sup>5</sup> The most severe complication is an LA to esophageal fistula, which is often fatal but quite rare. Another life-threatening complication is pericardial tamponade, but this can usually be treated with prompt pericardiocentesis. Clinically significant strokes and TIAs are observed in <1% of patients.<sup>1-4</sup> Deaths during ablations are typically from tamponade but may occur with strokes.<sup>1-4</sup>

Phrenic and vagal nerve paralysis are seen with cryoablation but are less common in radiofrequency ablation.<sup>2</sup> Early reports of PV stenosis were largely due to ablation inside the veins; with antral ablation this is rarely seen. The most common complications include bruising and bleeding at the vascular access site. Less common vascular complications include damage to the arterial or venous system or an atrioventricular fistula requiring surgery.

**8.5. Role of Pacemakers and ICDs for the Prevention and Treatment of AF**

Recommendations for the Role of Pacemakers and ICDs for the Prevention and Treatment of AF		
Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	A	1. In patients with bradycardia requiring cardiac-implanted electronic devices who have normal atrioventricular conduction, device selection and programming strategies to maintain atrioventricular synchrony and minimize ventricular pacing should be used to reduce the incidence and progression of AF. <sup>1-6</sup>
2b	B-NR	2. In selected patients with a pacemaker and symptomatic atrial tachyarrhythmias, antitachycardia atrial pacing and ventricular pacing minimization may be useful for reducing symptoms. <sup>7-13</sup>

(Continued)

Recommendations for the Role of Pacemakers and ICDs for the Prevention and Treatment of AF (Continued)		
COR	LOE	Recommendations
2b	C-LD	3. In patients with AF who require significant ventricular pacing, conduction system pacing may be useful to reduce progression of AF. <sup>14,15</sup>
3: No benefit	B-R	4. In patients with AF, specialized atrial pacing algorithms designed to suppress AF are not useful for reducing the incidence or slowing the progression of AF. <sup>12,16-18</sup>

### Synopsis

In patients with pacemakers, programming strategies to reduce RV pacing reduce the incidence of AF.<sup>1-6</sup> Because AF is observed in patients with symptomatic sinus node dysfunction who require permanent pacemakers for rate support, pacing algorithms were designed 20 to 30 years ago to suppress atrial ectopy but, unfortunately, no algorithm was able to successfully reduce AF in RCTs.<sup>12,16-19</sup> More recently, antitachycardia pacing algorithms have been designed to identify and terminate atrial arrhythmias and have been moderately effective in patients with arrhythmias associated with more organized atrial activation due to reentry.<sup>7-13</sup>

### Recommendation-Specific Supportive Text

- Several randomized and nonrandomized studies have shown that in patients who require cardiac-implanted electronic devices for sinus node dysfunction who have intact atrioventricular conduction, devices that maintain atrioventricular synchrony reduce the incidence and progression of AF.<sup>1-6</sup> Although maintenance of atrioventricular synchrony is important, post hoc analysis of MOST and a meta-analysis have demonstrated that the amount of ventricular pacing is an important contributor to the development of AF.<sup>6,20</sup> Algorithms designed specifically to reduce ventricular pacing reduced the incidence of AF in individual studies, but meta-analyses of RCTs suggests that the benefit may extend only to those patients with very infrequent pacing (<10%).<sup>19,21-23</sup> In the only randomized study that solely evaluated patients with atrioventricular block (and >70 years of age) who required permanent pacing, dual-chamber pacing did not reduce the incidence of AF when compared with single-chamber ventricular pacing.<sup>24</sup>
- Several studies have reported that specialized antitachycardia pacing algorithms can terminate atrial tachyarrhythmias but have not reduced AF burden.<sup>7-9</sup> However, in a post hoc analysis of a subset of patients who had high success rate of antitachycardia pacing ( $\geq 60\%$ ), antitachycardia pacing algorithms reduced the overall AF/AT burden from 2.5 hours/day to 0.68 hours/day ( $P < 0.01$ ).<sup>10</sup> A more recent study (MINERVA [Minimize Right Ventricular Pacing to Prevent Atrial Fibrillation and

Heart Failure]) found a modestly effective pacing algorithm that monitors for periods of regularization of atrial activity to initiate pacing algorithms reduced progression to persistent AF.<sup>11,12</sup> This algorithm may be more effective in patients who have undergone previous AF ablation.<sup>13</sup>

- Early nonrandomized evidence suggests that His bundle and left bundle pacing may reduce AF incidence and progression when compared with RV pacing in patients with high burden ventricular pacing.<sup>14,15</sup> In 1 study, left bundle branch area pacing reduced the incidence of new AF when compared with RV pacing, but this benefit was only evident in those patients with ventricular pacing >20%.<sup>14</sup> However, a meta-analysis that has evaluated all published evidence has only demonstrated a trend toward reduced AF. In 1 study, His bundle pacing reduced the likelihood of development of persistent AF in patients with sinus node dysfunction and a PR interval >180 ms.<sup>25</sup> There is indirect evidence for the potential benefit of the ventricular depolarization pattern for reducing AF because an algorithm that automatically adjusts pacing parameters based on intrinsic conduction has been associated with a decrease in longer AF episodes (>48 hours) when compared with conventional programming in a retrospective analysis.<sup>26-28</sup>
- Several studies have evaluated atrial pacing algorithms to reduce AF.<sup>12,16-19</sup> Pacing algorithms to minimize ventricular pacing in ATTEST (Atrial Therapy Efficacy and Safety Trial), a combination of algorithms designed to suppress AF and also provide antitachycardia pacing did not suppress atrial arrhythmias in patients with paroxysmal AF (AF frequency 1.3 episodes/month when "on" compared with 1.2 episodes/month when "off").<sup>8</sup> Despite optimistic results in some studies,<sup>12</sup> a meta-analysis found no benefit with atrial pacing algorithms for reducing the incidence of AF.<sup>19</sup>

## 8.6. Surgical Ablation

Recommendations for Surgical Ablation Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
2a	B-R	1. For patients with AF who are undergoing cardiac surgery, concomitant surgical ablation can be beneficial to reduce the risk of recurrent AF. <sup>1-3</sup>
2a	B-NR	2. In patients undergoing surgical ablation, anticoagulation therapy is reasonable for at least 3 months after the procedure to reduce the risk of stroke or systemic embolism. <sup>2-4</sup>
2b	B-R	3. For patients with symptomatic, persistent AF refractory to antiarrhythmic drug therapy, a hybrid epicardial and endocardial ablation might be reasonable to reduce the risk of recurrent atrial arrhythmia. <sup>5-7</sup>

## Synopsis

Among patients with AF or AFL, concomitant surgical ablation at the time of cardiac surgery has been shown to reduce the risk of recurrent atrial arrhythmia. However, it is associated with an increased risk of renal dysfunction and pacemaker placement. Among patients with symptomatic, persistent AF, a hybrid procedure combining epicardial and endocardial ablation has been shown to reduce the burden of atrial arrhythmia.

## Recommendation-Specific Supportive Text

1. The original atrial maze procedure consisted of a biatrial lesion set derived from a “cut-and-sew” technical approach.<sup>8</sup> Similar lesion sets delivered by cryoenergy or radiofrequency were subsequently developed. Surgical ablation concomitant with cardiac surgery currently takes place in approximately 1 in 5 patients with previous AF, most commonly at the time of a mitral valve procedure but also during aortic and tricuspid procedures or CABG.<sup>9</sup> In a Cochrane review of 22 clinical trials conducted between 1998 and 2013, there was evidence that surgical ablation is associated with increased freedom from AF, AFL, or AT (RR, 2.04 [95% CI, 1.63-2.55]). However, risk of pacemaker placement was increased (RR, 1.69 [95% CI, 1.12-2.54]).<sup>1,2</sup> A subsequent trial of patients undergoing mitral valve surgery with AF similarly found that ablation leads to increased freedom from AF at 1 year (63.2% versus 29.4%;  $P<0.001$ ) but with increased risk of pacemaker placement (21.5 versus 8.1 per 100 patient-years;  $P=0.01$ ).<sup>3</sup> Observational data suggest surgical ablation is associated with increased survival as well as risk of pacemaker placement and renal dysfunction.<sup>10-14</sup>
2. Two components of Virchow’s triad—endothelial injury and stasis of blood flow—can lead to a prothrombotic milieu in the context of surgical ablation. The former is a consequence of suture lines or ablation lesions, whether they result from radiofrequency or cryoenergy. The latter can occur with postcardioversion atrial stunning and/or atrial manipulation and consequent loss of mechanical function. Accordingly, trial protocols for several key studies of surgical ablation include the use of oral anticoagulation for at least 3 months after intervention.<sup>2,3</sup> Nonrandomized data suggest that stroke or systemic embolism in the first 3 months after catheter ablation is uncommon, but the risk increases with discontinuation of oral anticoagulation, especially in high-risk patients.<sup>4</sup> Patients who undergo surgical ablation may be at similar risk, and thus oral

anticoagulation, whether it be with warfarin or a DOAC<sup>15</sup> because appropriate accounting for concomitant indications such as a mechanical heart valve or mitral stenosis, should be initiated regardless of stroke risk when adequate surgical hemostasis has been achieved.

3. In a randomized trial of 149 patients with symptomatic and refractory AF, compared with catheter ablation, a hybrid procedure consisting of closed-chest, epicardial ablation combined with and followed by endocardial ablation led to increased freedom from atrial arrhythmias, including AF, AFL, and AT at 12 months (67.7% versus 50.0%;  $P=0.036$ ) at the expense of an increased risk of major adverse events such as stroke, bleeding, or pericardial effusion (0.0% versus 7.8%;  $P=0.0525$ ).<sup>16</sup> The ablation set of the hybrid procedure focused on surgical ablation of the LA posterior wall and PVI, while endocardial ablation completed PVI and addressed remaining gaps. Other observational studies of hybrid procedures with limited sizes show comparable rates of AF-free survival and safety.<sup>5-7</sup>

## 9. MANAGEMENT OF PATIENTS WITH HF

### 9.1. General Considerations for AF and HF

AF and HF frequently coexist, and either can predispose to the development of the other. Shared risk factors (eg, age, obesity, sedentary lifestyle, and hypertension) may contribute, as may atrial remodeling and diastolic dysfunction.<sup>1-3</sup> The prevalence of AF is higher in patients with heart failure with preserved ejection fraction compared with HFrEF.<sup>4</sup> In a recent study of the Framingham cohort, among individuals with new AF, more than one-third (37%) had HF.<sup>5</sup> Conversely, among individuals with new HF, more than half (57%) had AF. A meta-analysis, including 53 969 patients from 9 observational and 7 randomized trials, concluded that after adjusting for confounding factors, AF was associated with an increased total mortality, irrespective of LV systolic dysfunction, with an OR of 1.40 (95% CI, 1.32-1.48) in randomized trials and an OR of 1.14 (95% CI, 1.03-1.26) in observational studies.<sup>6</sup> The risk of mortality is higher when AF is incident after a diagnosis of HF as compared with prevalent AF, and in patients with HFrEF compared with heart failure with preserved ejection fraction.<sup>4,7-9</sup>

Special considerations for the management of patients with HF and AF are discussed in the next section on management of AF in HF, as well as in **Section 7.2 (“Specific Pharmacological Agents for Rate Control”)** and **Section 8.2 (“Electrical and Pharmacological Cardioversion”)**.

## 9.2. Management of AF in Patients With HF

Recommendations for Management of AF in Patients With HF* Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	B-NR	1. In patients who present with a new diagnosis of HFrEF and AF, arrhythmia-induced cardiomyopathy should be suspected, and an early and aggressive approach to AF rhythm control is recommended. <sup>1,2</sup>
1	A	2. In appropriate patients with AF and HFrEF who are on GDMT, and with reasonable expectation of procedural benefit (Figure 24), catheter ablation is beneficial to improve symptoms, QOL, ventricular function, and cardiovascular outcomes. <sup>3–13</sup>
2a	B-NR	3. In appropriate patients with symptomatic AF and HFpEF with reasonable expectation of benefit, catheter ablation can be useful to improve symptoms and improve QOL. <sup>14,15</sup>
2a	B-R	4. In patients with AF and HF, digoxin is reasonable for rate control, in combination with other rate-controlling agents or as monotherapy if other agents are not tolerated. <sup>16,17</sup>
2a	B-NR	5. In patients with AF and HF with rapid ventricular rates in whom beta blockers or calcium channel blockers are contraindicated or ineffective, intravenous amiodarone is reasonable for acute rate control. <sup>†18,19</sup>
2a	B-R	6. In patients with AF, HFrEF (LVEF <50%), and refractory rapid ventricular response who are not candidates for or in whom rhythm control has failed, AVNA and biventricular pacing therapy can be useful to improve symptoms, QOL, and EF. <sup>20–23</sup>
2a	B-NR	7. In patients with AF, HF, and implanted biventricular pacing therapy in whom an effective pacing percentage cannot be achieved with pharmacological therapy, AVNA can be beneficial to improve functional class, <sup>24,25</sup> reduce the risk of ICD shock, <sup>26</sup> and improve survival. <sup>24,25</sup>
2a	B-NR	8. In patients with AF-induced cardiomyopathy who have recovered LV function, long-term surveillance can be beneficial to detect recurrent AF in view of the high risk of recurrence of arrhythmia-induced cardiomyopathy. <sup>27,28</sup>
2b	B-NR	9. In patients with suspected AF-induced cardiomyopathy or refractory HF symptoms undergoing pharmacological rate-control therapy for AF, a stricter rate-control strategy (target heart rate <80 bpm at rest and <110 bpm during moderate exercise) may be reasonable. <sup>29–31</sup>
2b	C-LD	10. In patients with AF and HFrEF who undergo AVNA, conduction system pacing of the His bundle or left bundle branch area may be reasonable as an alternative to biventricular pacing to improve symptoms, QOL, and LV function. <sup>32–35</sup>
3: Harm	B-R	11. In patients with AF and known LVEF <40%, nondihydropyridine calcium channel-blocking drugs should not be administered because of their potential to exacerbate HF. <sup>36</sup>
3: Harm	B-R	12. For patients with AF, dronedarone should not be administered for maintenance of sinus rhythm to those with NYHA class III and IV HF or patients who have had an episode of decompensated HF in the past 4 weeks, due to the risk of increased early mortality associated with worsening HF. <sup>37</sup>

\*Please see other recommendations on anticoagulation in AF (Section 8.4.4, "Anticoagulation Therapy Before and After Catheter Ablation"), rate control in HF (Section 7, "Rate Control"), and agents for pharmacological cardioversion (Section 7.2, "Specific Pharmacological Agents for Rate Control") and maintenance of sinus rhythm (Section 8.3.1, "Specific Drug Therapy for Long-Term Maintenance of Sinus Rhythm"). †Consider the risk of cardioversion and stroke when using amiodarone as a rate-control agent.

### Synopsis

AF is the most common cause of arrhythmia-induced cardiomyopathy,<sup>27,38</sup> a condition where persistent AF, with or without rapid ventricular rates, can lead to LV dysfunction and HF that can be partially or completely reversed with adequate arrhythmia control.<sup>39</sup> AF can either be the only reason for cardiomyopathy (AF-induced) or can exacerbate LV dysfunction and HF in a patient with concomitant structural heart disease (AF-mediated).<sup>38,39</sup> Medical therapies for rate control (**Section 7**) or rhythm control (**Section 8**) of AF have special considerations in patients with HF based on differential safety. Routine pharmacological rhythm compared with rate control has not demonstrated benefit on clinical outcomes in patients with HFrEF,<sup>29,40</sup> although a recent subgroup analysis of patients with HF (most heart failure with preserved ejection fraction) demonstrated benefit of early rhythm control compared to rate control on clinical outcomes.<sup>1</sup> Several trials have compared AF catheter ablation with medical therapy in patients with HFrEF. Although earlier trials were small and focused on endpoints such as improvement in LVEF, QOL, and 6-minute walk, 2 of the largest trials have shown a benefit in reducing mortality rate and HF hospitalization.<sup>3–13</sup> Patients with AF and HF may undergo AVNA for rate control refractory to medical therapy.<sup>20,21</sup> Similar to findings in patients who undergo pacemaker implantation for conduction system disease, patients with HF appear to be more likely to develop or have worsened cardiomyopathy related to RV pacing dyssynchrony<sup>41,42</sup> and have improved outcomes with biventricular or conduction system pacing.<sup>23,32,33,35</sup>

### Recommendation-Specific Supportive Text

1. It can be difficult to determine the extent of the contribution of AF to cardiomyopathy and new onset HFrEF. Allowing AF to persist long term, regardless of reasonable rate control, may result in worsening HF and cardiomyopathy. An early and aggressive approach to rhythm control can reduce AF burden, resulting in favorable ventricular remodeling and halting of any occult arrhythmia-induced cardiomyopathy. In a prespecified subanalysis of 798 HF patients (NYHA class II/III or LVEF <50%) in EAST-AFNET (HFpEF, 442; midrange, 211; HFrEF [ $<40\%$ ], 132), early rhythm control significantly improved the composite outcome of death, stroke, or hospitalization for worsening of HF or for ACS (early rhythm control, 94/396; 5.7/100 patient-years) versus usual care (130/402; 7.9/100 patient-years; HR, 0.74 [95% CI, 0.56–0.97];  $P=0.03$ ), and this was not altered by HF status. Safety outcomes in each group were comparable. However, only 17% of the HF population had LVEF <40%.<sup>1</sup> In a post hoc analysis of the CASTLE-AF trial, an AF burden <50% at 6 months

postcatheter ablation was associated with significant improvement in the mortality rate and HF hospitalization in patients with AF and HFpEF.<sup>2</sup>

2. Multiple RCTs in HFpEF have shown that in patients with symptoms due to AF, ablation improves symptoms and QOL compared with a rate control or an antiarrhythmic drug strategy.<sup>3–13</sup> In each of 3 meta-analyses, QOL was improved.<sup>3,10,13</sup> Although in the past a trial of antiarrhythmic drugs was advised before pursuing catheter ablation, current data support ablation for AF as first-line therapy even before antiarrhythmic drugs; often patients require both. Data on LVEF, hospitalizations, and mortality rates are less robust, but nearly every larger RCT does show some benefit in these outcomes (Table 27). Characteristics that may identify patients with a higher likelihood of success or failure with AF catheter ablation are listed in Figure 24.<sup>43</sup>
3. Data for AF catheter ablation are far less robust for HFpEF. The largest analysis for this group of patients was a subanalysis of the CABANA trial of patients with HF; in this subgroup analysis, 778 patients (35% of the study population) enrolled in the study who had NYHA class II HF experienced improvement in survival, freedom from AF recurrence, and improved QOL compared with the medical therapy group.<sup>14</sup> Most of these had HFpEF. In this subanalysis, catheter ablation was associated with a reduction in the mortality rate and HF. A meta-analysis on catheter ablation in patients with HFpEF that included 7 studies and 764 patients showed the ablation to be safe and effective and associated with lower hospitalizations and the mortality rate.<sup>15</sup>
4. A small RCT in patients with persistent AF and HF (most HFpEF) compared the effects of digoxin, carvedilol, and the combination.<sup>16</sup> Combination therapy was associated with better rate control and symptom relief than monotherapy. The RATE-AF trial randomized 160 patients (≥60 years of age) with persistent AF and HF (81% with LVEF ≥50%) to digoxin or bisoprolol.<sup>17</sup> No significant difference was noted in the primary endpoint of QOL at 6 months. Secondary outcomes, including natriuretic peptide levels, were significantly lower in the digoxin group, without a significant difference in resting heart rate at 12 months. Adverse effects were less common in the digoxin group. Observational and post hoc analyses have suggested an excess mortality with digoxin in patients with AF; however, residual confounding due to the use of digoxin in sicker patients may have a role.<sup>44</sup> In patients with HF on digoxin chronically, post hoc analyses have suggested increased mortality rates and hospitalization with serum digoxin levels ≥1 ng/mL; levels <0.8 ng/mL in HF were associated

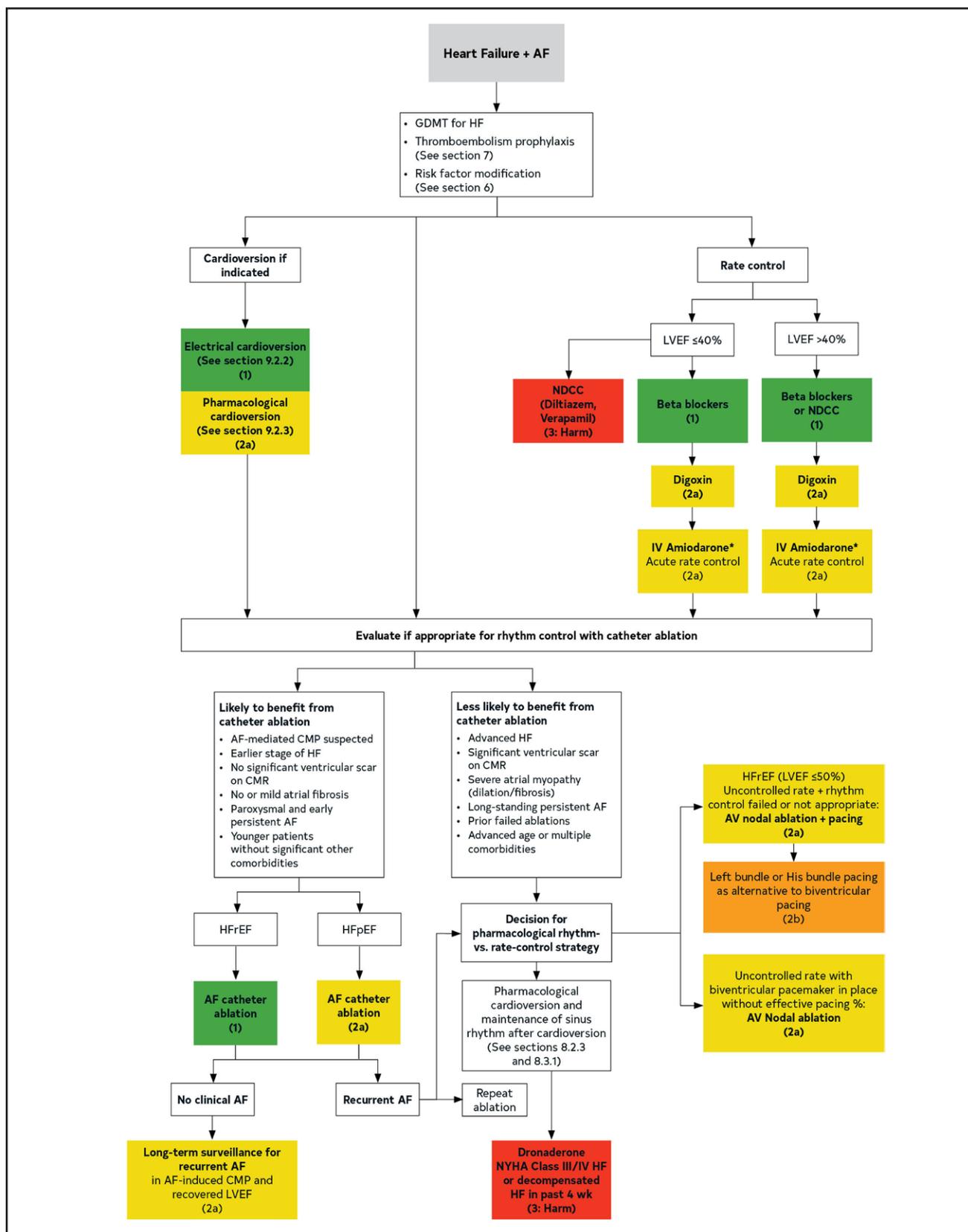
with the lowest mortality rate, although the study was for therapy of HF and not AF.<sup>45</sup> In the DAAF (Digitalis in Acute Atrial Fibrillation) trial of 239 patients (12% with HF), intravenous digoxin led to a significant decrease in heart rate at 2 hours compared with placebo.

5. In trials of critically ill patients, some of which included a smaller proportion of patients with HF, intravenous amiodarone has been shown to be effective in controlling ventricular rates.<sup>18,19,46</sup> In a randomized trial of 60 such patients (13 with HF), significant rate control was achieved with both intravenous diltiazem and intravenous amiodarone. However, intravenous diltiazem was associated with a significantly higher frequency of hypotension requiring discontinuation.<sup>19</sup> In another retrospective study of 38 patients admitted to the intensive care unit (9 with HF), intravenous amiodarone was associated with a statistically significant decrease in ventricular rate without decrease in BP (and in some cases improved hemodynamics) compared with intravenous diltiazem and digoxin.<sup>18</sup> Intravenous beta blockers may also cause hypotension and may not be tolerated in patients with HF and hemodynamic instability. Although less frequent, intravenous amiodarone can also be associated with hypotension, specifically with the intravenous bolus. The possibility of conversion to sinus rhythm with intravenous amiodarone and associated potential for thromboembolism, especially in patients with longer-standing AF not on anticoagulation, should factor into the risk-benefit decision when intravenous amiodarone is chosen for rate control.
6. Small RCTs of patients with medically refractory AF and HF show that patients who undergo AVNA and conventional pacemaker implantation are less symptomatic and have improvements in QOL and exercise tolerance compared with subjects who are managed with medical rate control.<sup>20–22,47</sup> A meta-analysis comparing outcomes with AVNA or medications showed, in 2 studies analyzing patients with reduced EF, a modest, yet significant +4% increase in EF in patients undergoing AVNA and RV pacing, while patients with normal EF at baseline did not show a significant change.<sup>48</sup> A meta-analysis of 93 studies including 11 343 patients who underwent AVNA with either RV pacing or biventricular pacing showed periprocedural complications of arrhythmia, HF, and lead dislodgement in 2% to 2.5%,<sup>49</sup> few long-term data, and worse outcomes in younger patients with reduced EF and RV pacing.<sup>49</sup> Overall, these data showed improved mortality in patients with HF who are treated with cardiac resynchronization therapy (CRT), at the risk of increased device-related complications.<sup>49</sup> The

**Table 27. Randomized Trials of Rhythm Control in HF**

Study/ Author (y)	No. Pts.	Inclusion	Exclusion	Intervention	Primary Outcome	Death and Hospitalization	Death	Hospitalizations	Reduction in AF	LVEF	QOL	6MWT	Peak VO <sub>2</sub> Max	BNP
Roy (2008) <sup>60</sup>	1376	LVEF <35%, CHF		AAD (primarily amiodarone) vs rate control	Cardiovascular mortality was no different between rhythm vs rate control	No change	No difference	No difference						
MacDonald (2011) <sup>8</sup>	41	Persistent AF; LVEF <35%, CHF II-IV	PAF; QRS >150	RF to medical therapy	Similar increase in CMR LVEF			No difference	Improved with RF	Improved	No change	No change		
ARC-HF: Jones (2013) <sup>9</sup>	52	Persistent AF; LVEF <35%, CHF		RF to medical therapy	Improvement in peak VO <sub>2</sub> with RF	No change	No difference	No difference		No change	Improved with RF	No change	Improved	
CAMTAF (2014) <sup>5</sup>	50	Persistent AF; LVEF <50%; CHF		RF to medical therapy	LVEF significantly improved with RF	No change	No difference			Improved	Improved with RF		Improved	
AATAC (2016) <sup>4</sup>	203	Persistent AF; LVEF <40%, CHF II-III		RF to amiodarone	At 24 mo, RF patients more likely to be in NSR	Improvement with RF	Improved	Improved		Improved	Improved with ablation	Improved		
CAMERA MRI (2017) <sup>12</sup>	66	Persistent AF; LVEF <45%, CHF II-III; idiopathic CM		RF to medical therapy	Improved LVEF with RF					Improved	No change	No change		Improved
CASTLE-AF (2018) <sup>9</sup>	363	PAF or persistent AF; LVEF <36%, CHF II-IV and ICD		RF to medical therapy	Composite of death and hospitalization lower with RF	Improvement with RF	Improved	Improved		Improved				
AMICA (2019) <sup>7</sup>	140	Persistent AF; LVEF <36%		RF to medical therapy	No difference in change in LVEF					No change	No change	No change		No change
CABANA substudy (2021) <sup>14</sup>	778	Clinical HF (largely HFpEF)		RF to medical therapy	Decrease in composite of MACE		Improved		Improved with RF		Improved with RF			
RAFT-AF (2022) <sup>11</sup>	411	≥4 PAF/y or persistent AF, NYHA class II or III HF, elevated pro-BNP		RF to medical therapy	No difference in change in mortality/HF	No difference in change in mortality/HF	No change	No change	Improved with RF	Improved with RF	Improved with RF	Improved with RF		Improved with RF
Meta-analysis-Turagam (2019) <sup>13</sup>	775			RF to medical therapy			Improved	Reduced		Improved	Improved	Improved	Improved	
Meta-analysis-Chen (2020) <sup>5</sup>	1112			RF to medical therapy			Improved	Reduced	Improved with RF	Improved	Improved			
Meta-analysis-Pan (2021) <sup>10</sup>	775			RF to medical therapy			Improved	Reduced		Improved	Improved	Improved		

AAD indicates antiarrhythmic drug; AATAC, Ablation vs Amiodarone for Treatment of Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted ICD/CRTD; AF, atrial fibrillation; AMICA, Atrial Fibrillation Management in Congestive Heart Failure With Ablation; ARC-HF, A Randomised Trial to Assess Catheter Ablation Versus Rate Control in the Management of Persistent Atrial Fibrillation in Chronic Heart Failure; BNP, brain natriuretic peptide; CABANA, Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation; CAMERA MRI, Catheter Ablation versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction-an MRI-Guided Multi-centre Randomised Controlled Trial; CAMTAF, Catheter Ablation Versus Medical Treatment of AF in Heart Failure; CASTLE-AF, Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation; CHF, congestive heart failure; CM, cardiomyopathy; CMR, cardiac magnetic resonance; HF, heart failure; HFpEF, heart failure with persistent ejection fraction; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; NSR, normal sinus rhythm; NYHA, New York Heart Association; PAF, paroxysmal atrial fibrillation; QOL, quality of life; RAFT-AF, Rhythm Control-Catheter Ablation With or Without Anti-arrhythmic Drug Control of Maintaining Sinus Rhythm Versus Rate Control With Medical Therapy and/or Atrio-ventricular Junction Ablation and Pacemaker Treatment for Atrial Fibrillation; RF, radiofrequency; VO<sub>2</sub> max, maximal oxygen consumption; and 6MWT, 6-minute walk test.



**Figure 24. Management of Patients With HF and AF.**

Colors correspond to Table 2. AF indicates atrial fibrillation; AV, atrioventricular; CMP, cardiomyopathy; CMR, cardiac magnetic resonance; GDMT, guideline-directed medical therapy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; IV, intravenous; LVEF, left ventricular ejection fraction; NDCC, nondihydropyridine calcium channel blocker; and NYHA, New York Heart Association.

- AAPAF-CRT (Ablate and Pace in Atrial Fibrillation plus Cardiac Resynchronization Therapy) mortality trial of 133 subjects with AF, HF, and narrow QRS was stopped early due to a HR of 0.26 for all-cause mortality, also suggesting that when AVNA is performed in patients with HF, CRT is preferable to conventional RV pacing.<sup>23</sup> Data are accumulating regarding similarly improved outcomes with conduction system pacing compared with conventional RV pacing in this population.<sup>32–35</sup>
7. Conduction of AF may hinder delivery of biventricular pacing therapy (CRT) and worsen outcomes.<sup>25</sup> Initial clinical trials of CRT included low numbers of patients with AF,<sup>50</sup> and observational analyses suggested a reduced benefit of CRT in patients with AF due to ineffective biventricular pacing.<sup>51,52</sup> A systematic review to evaluate the impact of AVNA in patients with AF and CRT found AVNA was associated with significant reductions in all-cause mortality (RR, 0.42 [95% CI, 0.26–0.68]), cardiovascular mortality (RR, 0.44 [95% CI, 0.24–0.81]), and improvement in NYHA class (RR, –0.52 [95% CI, –0.87 to –0.17]).<sup>24</sup> Confirmatory evidence of the importance of adequate biventricular pacing percentage is provided by an analysis of remote monitoring data showing a strong association between increasing percentages of biventricular pacing and reduced mortality, with the greatest magnitude reduction at >98% pacing.<sup>53</sup> In a systematic review and meta-analysis of 31 studies in 83 571 individuals, CRT alone did not improve the mortality rate in patients with AF, but the all-cause mortality rate was lower in the AVNA group.<sup>25</sup> Many patients with CRT devices also have combined defibrillator therapy. In a pooled analysis of 664 patients with AF and CRT in whom 282 underwent AVNA, a significant reduction in appropriate and inappropriate ICD shocks and a decrease in all-cause hospitalizations was associated with AVNA.<sup>26</sup>
  8. In an observational study of 24 patients with AF-induced cardiomyopathy and NYHA class III/IV HF, the median time from onset of arrhythmia to cardiomyopathy and HF was 4.2 years. Aggressive rate/rhythm control resulted in significant LVEF recovery in all patients within 6 months. Five of 24 patients had recurrent AF, and all had a rapid decline in LVEF within 6 months after arrhythmia recurrence.<sup>27</sup> In an observational cohort of 69 patients with AF and LVEF <40% who underwent catheter ablation, patients who maintained sinus rhythm (65%) had complete LV function recovery and maintained normal LVEF over 28±11 months of follow-up, compared with those who had recurrent AF/AT.<sup>28</sup> Long-term surveillance to detect recurrent AF can be beneficial and can be accomplished by various modalities, including wearable devices, smart watches, random monitoring (Holter, event, mobile telemetry), and implantable loop recorders.
  9. In patients with arrhythmia-induced cardiomyopathy and HFrEF, the ideal target heart rate for rate control remains uncertain. However, because of the potential negative impact of rapid ventricular rates on HF and cardiomyopathy, a stricter rate-control strategy may be reasonable. In the AF-CHF trial, which compared rate control versus rhythm control using antiarrhythmic therapy in AF and HFrEF, the target rate control was defined as ventricular rate <80 bpm during resting 12-lead electrocardiography and <110 bpm during a 6-minute walk test.<sup>29</sup> In the RACE II trial, 614 patients with permanent AF were randomized to a heart rate <80 bpm at rest and <110 bpm during moderate exercise or lenient control (resting heart rate, <110 bpm), with results showing similar outcomes in each arm. However, RACE II trial patients were rate controlled at enrollment (baseline heart rate, 96 bpm), and only 15% of the study cohort had an LVEF <40%, plus very few patients had heart rates >100 bpm, even in the lenient rate control group.<sup>54</sup> In a crossover study of 20 patients with persistent AF and LVEF <40%, patients were given escalating doses of metoprolol (average dose, 121 mg) to get target heart rate <70 bpm. After 3 months, average resting heart rate decreased from 94±14 bpm to 85±12 bpm, but no significant differences in QOL on functional status were noted.<sup>31</sup> Strict rate control is also advisable in patients with ICDs and CRT (**See Table 20 in Section 7.1, “Broad Considerations for Rate Control”**).<sup>55,56</sup>
  10. In small observational series of patients undergoing AVNA and His bundle pacing, postprocedural increase in EF and improved functional class has been demonstrated, at the expense of increased pacing thresholds in some patients.<sup>32,35</sup> A single-center study comparing outcomes after AVNA with His bundle pacing and left bundle area pacing in 105 patients showed a higher rate of recurrent AVN conduction in the His bundle pacing group and longer fluoroscopy time.<sup>33</sup> Acute threshold rise, exit block, and elevated long-term thresholds were also seen in the His bundle pacing group but not in left bundle area pacing in follow-up limited to 10.5 months. Both strategies were associated with a significantly improved EF in patients with EF <50% at baseline (N=16; 37%±7.6% versus 46%±13%; *P*=0.02).<sup>33</sup> An observational comparative study of patients undergoing AVNA, of whom 113 had RV (56) or BiV (57) pacing and 110 had conduction system pacing (84 His bundle pacing and 46 left bundle area pacing) showed increased

EF in conduction system pacing compared with the mixed RV/BivP group ( $46.5\% \pm 14.2\%$  to  $51.9\% \pm 11.2\%$ ;  $P=0.02$ ) in conduction system pacing and  $36.4\% \pm 16.1\%$  to  $39.5\% \pm 16\%$  ( $P=0.04$ ) in RV/BiVP.<sup>34</sup> A combined endpoint of time to death or HF hospitalization was reduced in the conduction system pacing group in  $>2$  years of follow-up, but extrapolation is limited due to the observational and selected nature of the population and because the RV/BiVP group had lower EF and wider QRS at baseline.<sup>34</sup>

11. The nondihydropyridine calcium channel blockers—diltiazem and verapamil—are negative inotropic agents and may not be tolerated in patients with HFrEF. In the acute setting, limited data from 2 retrospective analyses suggest the potential for increased morbidity with the use of diltiazem in patients with HFrEF, including worsening HF, need for inotropic support, or acute kidney injury.<sup>57,58</sup> In the chronic setting, diltiazem had no impact on mortality in a trial of patients with nonischemic cardiomyopathy.<sup>59</sup> However, in the multicenter randomized MDPIT of patients postacute MI, HF and cardiac events (cardiac death or nonfatal reinfarction) were more frequent in the patients with LVEF  $<40\%$  or pulmonary congestion who were randomized to diltiazem. Among those with a baseline EF of  $<40\%$ , late HF appeared in 12% receiving placebo and 21% receiving diltiazem ( $P=0.004$ ). Life table analysis in patients with an EF of  $<40\%$  confirmed more frequent late HF in those taking diltiazem ( $P=0.0017$ ). In addition, the diltiazem-associated increase in the frequency of late HF was progressively greater with decreasing baseline EF.<sup>36</sup> This increase in late HF was not seen in patients with pulmonary congestion at baseline but an EF of  $\geq 40\%$ , suggesting the association of diltiazem-related late HF was present only in those with systolic LV dysfunction.
12. The ANDROMEDA<sup>37</sup> study was a randomized, double-blind placebo-controlled study that tested the hypothesis that dronedarone would reduce the rate of hospitalization due to HF and possibly reduce mortality by reducing the incidence of arrhythmic death. The study enrolled patients who were hospitalized with new or worsening HF and who had at least 1 episode of NYHA class III or IV HF (shortness of breath on minimal exertion or at rest). More than 40% of the patients had NYHA class II HF at baseline. The investigators reported that, contrary to the study's hypothesis, mortality was higher in the dronedarone group compared to that in the placebo group (8.1% versus 3.8%; HR, 2.13 [95% CI, 1.07–4.25];  $P=0.03$ ). The excess mortality was principally associated with worsening HF.

## 10. AF AND SPECIFIC PATIENT GROUPS

### 10.1. Management of Early Onset AF, Including Genetic Testing

Recommendations for Management of Early Onset AF, Including Genetic Testing		
Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
2b	B-NR	1. In patients with an onset of unexplained AF before 30 years of age, electrophysiological study to evaluate and treat reentrant supraventricular tachyarrhythmias with a targeted ablation may be reasonable because of the high prevalence of reentrant arrhythmias in this group. <sup>1–3</sup>
2b	B-NR	2. In patients with an onset of AF before 45 years of age without obvious risk factors for AF, referral for genetic counseling, genetic testing for rare pathogenic variants, and surveillance for cardiomyopathy or arrhythmia syndromes may be reasonable. <sup>4,5</sup>

#### Synopsis

Young patients are less likely to develop AF or associated strokes compared with older populations. Consumer-driven use of wearable devices is increasing and can lead to the diagnosis of AF at a young age.<sup>6</sup> In those  $<30$  years of age, reentrant SVTs (atrioventricular nodal reentrant tachycardia and atrioventricular reentrant tachycardia) are found in about 25% of patients.<sup>1–3</sup> Targeted ablation of the reentrant tachycardia is followed by resolution of AF episodes in most of these young patients. However, additional factors need to be taken into consideration in young patients who present with AF. Growing evidence suggests that, in addition to risk factors for AF present in older populations, young patients who develop AF may also harbor susceptibility for inherited ion channel and cardiomyopathic disorders,<sup>4</sup> even in those with normal echocardiograms.<sup>5</sup> In addition to the standard workup for newly diagnosed AF, genetic testing for rare pathogenic variation, advanced imaging modalities, and surveillance screening could detect otherwise occult cardiomyopathy.

#### Recommendation-Specific Supportive Text

1. Two retrospective observational cohort studies included patients with onset of AF before the age of 21 years<sup>2</sup> and 30 years<sup>1</sup> who underwent electrophysiological study to assess for reentrant SVTs. The former study found atrioventricular node reentry tachycardia or atrioventricular reentry tachycardia in 39% of patients and the latter in 24%. In both studies, after targeted ablation of the reentry tachycardia, patients were observed for recurrence of AF for a median of about 1.5 years. The former study reported no recurrences of AF, and the latter study reported that 86% remained free of atrial arrhythmias. In an additional prospective cohort study of patients referred for AF ablation who had inducible atrioventricular node reentry tachycardia,

12 of 13 patients who underwent slow pathway ablation without PVI had no recurrence of AF after a mean follow-up of 21 months.<sup>3</sup>

2. A prospective observational cohort study in patients with AF diagnosed before the age of 66 years and who had sequencing of genes typically found in ion channelopathy and cardiomyopathy panels reported that among 1293 patients studied, 10% (131) were found to have a disease-associated variant, primarily in cardiomyopathy-related genes.<sup>4</sup> In 1 study of 23 unrelated patients with onset of AF at <45 years of age who had a normal echocardiogram and no other readily identifiable causes of AF, 24% had a pathogenic or likely pathogenic variant identified. Most of these were also in cardiomyopathy-related genes.<sup>5</sup>

## 10.2. Athletes

Recommendation for Athletes		
Referenced studies that support the recommendation are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendation
2a	B-NR	1. In athletes who develop AF, catheter ablation with PVI is a reasonable strategy for rhythm control because of its effectiveness and low risk of detrimental effect on exercise capacity. <sup>1,2</sup>

### Synopsis

Engaging in moderate levels of exercise has several cardiovascular benefits and, in some studies, has been associated with a lower incidence of AF.<sup>3,4</sup> However, high-volume endurance athleticism, defined here as exercise of >45 metabolic equivalent-hours per week, has been associated with a higher prevalence of AF,<sup>5</sup> particularly in young athletes.<sup>6</sup> The mechanisms behind this association are not well established but may be related to atrial myopathy from exercise-induced stretch or perhaps inflammation.<sup>7,8</sup> No studies have prospectively studied the effects of detraining on AF burden, but some have proposed that moderation of exercise may be considered, although it is unclear whether changes are reversible.<sup>9</sup> Nevertheless, athletes will often choose to continue sport participation, and aggressive rhythm control strategies are often sought. Because many of these patients are young, medications are often not tolerated or preferred. PVI has been shown to be safe and effective in this population without resulting in a significant reduction in exercise capacity<sup>1</sup> and has been shown to significantly improve QOL.<sup>2</sup>

### Recommendation-Specific Supportive Text

1. In a prospective cohort study of 144 athletes, AF ablation with PVI, including multiple procedures, resulted in freedom from AF at 1 year in 86% of athletes with paroxysmal AF and 68% of athletes with persistent AF over a median follow-up of 3 years.<sup>1</sup> Athletes underwent cardiopulmonary

exercise stress testing before and after ablation and, although the sinus rate increased on average 10 bpm after ablation (which may bother some athletes and thus should be discussed before the procedure), no significant changes were observed in maximum metabolic equivalents on exercise treadmill testing. In a retrospective cohort study of 133 competitive athletes who underwent catheter ablation for AF with 10-year follow-up, 83% of athletes did not have recurrent events and had significantly improved QOL scores.<sup>2</sup>

## 10.3. Management Considerations in Patients With AF and Obesity

Obesity is a strong risk factor for AF.<sup>1</sup> In the Framingham Study, overweight and obesity increased the risk of incident AF, with a 4% increase in AF risk per unit increase in BMI in men and women. Adjusted HRs for AF associated with obesity were 1.52 (95% CI, 1.09-2.13;  $P=0.02$ ) and 1.46 (95% CI, 1.03-2.07;  $P=0.03$ ) for men and women, respectively, compared with individuals with normal BMI. In that study, the excess risk of AF associated with obesity appeared to be mediated through LA dilatation.<sup>2</sup> Other studies suggest that the risk of AF with obesity is mediated through epicardial and abdominal fat, or structural changes in the atria.<sup>1,3</sup> Obesity is also associated with other comorbidities, including hypertension, HF, and sleep apnea, which themselves predispose to an increased incidence of AF. Further, higher BMI and obesity are associated with an increase in the burden of AF, including progression from paroxysmal to permanent AF, and an increased risk of AF recurrence after AF ablation.<sup>4</sup> Special considerations for the management of AF in patients with obesity include the role of weight loss in the primary and secondary prevention of AF (**Section 5, “Lifestyle and Risk Factor Modification for AF Management”**), as well as anticoagulation in patients with severe or class III obesity in this section and in **Section 10.4 (“Anticoagulation Considerations in Patients With Class III Obesity”)**.

## 10.4. Anticoagulation Considerations in Patients With Class III Obesity

Recommendations for Anticoagulation Considerations in Patients With Class III Obesity		
Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
2a	B-NR	1. In patients with AF and class III obesity (BMI $\geq$ 40 kg/m <sup>2</sup> ), DOACs are reasonable to choose over warfarin for stroke risk reduction. <sup>1-5</sup>
2b	C-LD	2. In patients with AF who have undergone bariatric surgery, warfarin may be reasonable to choose over DOACs for stroke risk reduction in view of concerns about DOAC drug absorption. <sup>6,7</sup>

**Synopsis**

Patients with class III obesity (BMI ≥40 kg/m<sup>2</sup>) are underrepresented in the major clinical trials evaluating the efficacy and safety of DOACs in patients with AF. Post hoc analyses of major DOAC trials in AF and large observational studies have shown comparable efficacy and safety of DOACs compared with warfarin across weight groups, including patients with class III obesity.<sup>1-5</sup> Thus, DOACs are preferred over warfarin for stroke risk prevention in patients with class III obesity and AF. Little evidence is available that evaluates the pharmacokinetics, efficacy, and safety of DOACs in patients with AF who have undergone bariatric surgery. Thus, warfarin may be reasonable to choose over DOACs to reduce stroke risk in this population until further data become available.

**Recommendation-Specific Supportive Text**

1. Post hoc analyses of the ARISTOTLE (apixaban versus warfarin), ROCKET AF (rivaroxaban versus warfarin), and ENGAGE AF-TIMI 48 (edoxaban versus warfarin) demonstrated consistent efficacy (stroke and systemic embolism) and safety (major bleeding) of DOACs compared with warfarin across weight groups in patients with AF.<sup>3-5</sup> A meta-analysis including these trials and RE-LY (dabigatran versus warfarin) again showed similar efficacy and safety of DOACs compared with warfarin, although the outcome differences were attenuated in obese patients.<sup>2</sup> A large retrospective observational study including 36094 patients compared risk of ischemic stroke, significant bleeding, and mortality in patients receiving a DOAC or warfarin, stratified by BMI group.<sup>1</sup> For all 3 endpoints, better outcomes were observed with DOACs across BMI groups. In patients with a BMI ≥40 kg/m<sup>2</sup>, a relative risk reduction of 25% for ischemic stroke (adjusted HR, 0.75 [95% CI, 0.64-0.87]; *P*<0.001), 57% for significant bleeding (adjusted HR, 0.43 [95% CI, 0.20-0.94]; *P*<0.001), and 34% for all-cause mortality (adjusted HR, 0.66 [95% CI, 0.56-0.77]; *P*<0.001) was observed with DOACs compared with warfarin.
2. Although case reports exist that demonstrate expected factor Xa trough levels in patients taking a DOAC who undergo bariatric surgery, a meta-analysis of cohort studies, case series, and case reports has shown that 42% of patients who have undergone bariatric surgery had peak drug levels below the expected range.<sup>6,7</sup> Patients who have undergone bariatric surgery are not well represented in any of the major trials comparing DOACs with warfarin, and few observational data support DOAC use in this population. Warfarin's therapeutic effect can be routinely monitored. Thus, in patients

with AF who have undergone bariatric surgery, warfarin may be a reasonable choice over DOACs for stroke risk reduction at this time.

**10.5. AF and VHD**

VHD and AF commonly coexist. AF independently predicts the risk of cerebrovascular events among patients with valve disease.<sup>1</sup> This risk may be addressed with the use of oral anticoagulation, percutaneous and surgical LAAO, and surgical ablation as described in **Sections 6.5.1 (“Percutaneous Approaches to Occlude the LAA”), 6.5.2 (“Cardiac Surgery—LAA Exclusion/Excision”), and 6.8.5 (“AF in VHD”).**

**10.6. WPW and Preexcitation Syndromes**

Recommendations for WPW and Preexcitation Syndromes		
Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	B-NR	1. Patients with AF with rapid anterograde conduction (preexcited AF), and hemodynamic instability should be treated with electrical cardioversion. <sup>1,2</sup>
1	B-NR	2. For patients with AF with rapid anterograde conduction (preexcited AF), catheter ablation of accessory pathways (APs) is recommended. <sup>3-7</sup>
1	C-LD	3. In patients with AF with rapid anterograde conduction (preexcited AF) and hemodynamic stability, pharmacological cardioversion with intravenous ibutilide or intravenous procainamide is recommended as an alternative to elective cardioversion. <sup>1,8,9</sup>
3: Harm	B-NR	4. For patients with AF with anterograde accessory pathway conduction (preexcited AF), pharmacological agents that block atrioventricular nodal conduction (verapamil, diltiazem, amiodarone, digoxin, adenosine, or beta blockers) are contraindicated due to risk of precipitating VF or hemodynamic deterioration. <sup>10-14</sup>

**Synopsis**

WPW and preexcitation syndromes refer to the presence of extra-atrioventricular nodal connection(s) between atrium and ventricle; such APs are comprised of atrial tissue.<sup>15</sup> AF occurs in approximately 15% of persons with WPW and although the mechanism(s) remain unclear, the faster conduction properties of atrial tissue compared with the atrioventricular node allow for rapid rates in preexcited AF.<sup>15-17</sup> The risk of preexcited AF is higher for those with multiple pathways and short anterograde pathway refractory period (<250 ms), which allows rapid conduction and predisposes to VF and sudden death.<sup>1,18,19</sup> Moreover, AF in young persons without evidence of comorbid conditions may be associated with an AP, and pathway ablation is definitive therapy for AF and SVT in these persons.<sup>1</sup> For those who cannot undergo ablation, preventive pharmacological therapy is directed to slowing pathway conduction.<sup>20,21</sup>

### Recommendation-Specific Supportive Text

1. Preexcited AF can conduct rapidly over the pathway and lead to VF. During an acute episode of preexcited AF with rapid ventricular response and hemodynamic instability, electrical cardioversion must be used to restore sinus rhythm.<sup>1,2</sup>
2. Pathway ablation has well-established efficacy and safety for those with preexcited AF for prevention of VF.<sup>1</sup> Multiple large-patient series point to a high success rate (93%-95%) balanced with low risk of major short- and long-term complications.<sup>3-7</sup> Electrophysiological study and AP ablation can be offered as first-line therapy.
3. Pharmacological treatments that increase the refractory period of atrial tissue (ie, ibutilide or procainamide) can slow AP conduction and terminate AF. Hemodynamically stable patients presenting with preexcited AF with or without rapid ventricular rates can be pharmacologically managed with such agents.<sup>8,9</sup> In 1 study involving 22 patients, ibutilide terminated AF in 21 patients and prolonged refractoriness of the atrioventricular node, His-Purkinje system, and AP.<sup>9</sup>
4. AP conduction can accelerate with atrioventricular nodal block. Administration of pharmacological agents that block atrioventricular nodal conduction can increase the risk of VF. The use of atrioventricular nodal blocking agents for patients with preexcited AF are potentially harmful due to the risk of accelerated pathway conduction and associated VF.<sup>1,10-12</sup> One small series that reviewed intravenous amiodarone for this indication raised significant concerns in view of several published reports on instances of VF precipitated by amiodarone.<sup>13</sup> In 1 study of patients with WPW who received verapamil during electrophysiological study, verapamil decreased the shortest RR interval between preexcited ventricular complexes during AF, and 2 patients deteriorated and required cardioversion.<sup>14</sup> Data are very limited and observational, but because other safer options are readily available, atrioventricular nodal agents are best avoided in this setting.

### 10.7. Hypertrophic Cardiomyopathy

The “AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy” was published in December 2020, and this guideline included recommendations on AF.<sup>1</sup> Data on AF in patients with HCM published since the 2020 hypertrophic cardiomyopathy guideline were reviewed but did not result in any substantive changes in the recommendations from 2020.<sup>2-6</sup> AF is highly prevalent in HCM and increases the risk of stroke. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score

should not apply to patients with HCM, because they have roughly an equivalent risk to a CHADs-VASc of 3. Data on the use of DOACs in patients with HCM suggest these to be acceptable alternatives to warfarin. When a rhythm-control strategy is needed, several antiarrhythmic drugs have been shown to be safe and effective, allowing for individualization according to underlying substrate and patient preference. Catheter ablation is also an important option, although more confirmatory studies have shown AF ablation is of lower success compared with patients without HCM.<sup>7</sup> For specifics, please see the “2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy.”<sup>1</sup>

### 10.8. Adult Congenital Heart Disease (ACHD)

Recommendations for ACHD		
Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	B-NR	1. In adults with congenital heart disease and AF, it is recommended to evaluate for and treat precipitating factors and reversible causes of AF, recognizing that residual hemodynamic sequelae may contribute to the occurrence of the arrhythmia. <sup>1,2</sup>
1	C-LD	2. In adults with AF and moderate or complex congenital heart disease, electrophysiological procedures should be performed by operators with expertise in ACHD procedures and in collaboration with an ACHD cardiologist, ideally in specialized centers, when available. <sup>3-5</sup>
1	C-LD	3. In adults with congenital heart disease and symptomatic or hemodynamically significant paroxysmal or persistent AF, an initial strategy of rhythm control is recommended regardless of lesion severity as AF in this population is often poorly tolerated. <sup>6</sup>
2a	B-NR	4. In symptomatic patients with simple congenital heart disease with antiarrhythmic drug-refractory AF, it is reasonable to choose ablation over long-term antiarrhythmic therapies. <sup>4,7</sup>
2b	C-LD	5. In adults with congenital heart disease with AF undergoing PVI, it may be reasonable to include an ablative strategy in the right atrium directed at reentrant arrhythmia secondary to atriotomy scars and the CTI. <sup>8,9</sup>
2b	C-LD	6. In adults with AF and moderate or severe forms of congenital heart disease, particularly those with low-flow states such as Fontan circulation, blind-ending cardiac chambers, and cyanosis, it may be reasonable to treat with anticoagulation independent of conventional risk score to reduce risk of thromboembolic events. <sup>10</sup>

#### Synopsis

Atrial arrhythmias are a leading cause of morbidity in adults with congenital heart disease, and AF surpasses intra-atrial reentrant tachycardia in patients with CHD >50 years of age.<sup>11</sup> Risk factors for development of AF in patients with ACHD are similar to those for the general population; however, the presence of an atrial

septal defect is an independent risk factor. Adults may be classified as having simple, moderate, or complex forms of CHD, based on a classification proposed in the “2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease.”<sup>12</sup> Choosing pharmacological therapy for treatment of patients with ACHD who have AF should consider factors such as coexisting sinus node dysfunction or atrioventricular block, as well as the ventricular function and other comorbidities. Ablation strategies established in normal hearts can be applied to patients with simple forms of CHD; however, caution must be taken in those patients with moderate or complex forms of ACHD.<sup>13</sup> Knowledge of the underlying congenital anatomy is key, because access to the atrial chambers may require specialized approaches. In those patients with moderate or complex forms of CHD, electrophysiological procedures should be performed by operators with expertise in CHD and in collaboration with an ACHD cardiologist.<sup>3</sup>

### Recommendation-Specific Supportive Text

- Adults with CHD often have hemodynamic sequelae of childhood repair, and any new onset arrhythmia, including AF, should prompt an evaluation for treatable and reversible causes. Studies have shown that AF is correlated with RA dilation, thus necessitating addressing the underlying substrate in addition to treating the arrhythmia.<sup>1,2</sup>
- Patients with ACHD who are undergoing invasive electrophysiological procedures in specialized ACHD centers generally have better outcomes, including survival, than those managed in other care settings.<sup>3–5</sup> Special attention is required to ensure appropriate periprocedural care, including identification of procedure-related risk factors and availability of ancillary imaging.<sup>12</sup>
- Adults with simple forms of CHD and AF are generally managed according to standard published guidelines. In those patients with moderate or complex forms of CHD, choice of antiarrhythmic therapy should be individualized.<sup>6</sup> Most antiarrhythmic drugs are associated with proarrhythmic effects and increased mortality in ACHD patients.<sup>14</sup> Rhythm control is generally preferred over rate control in patients with ACHD with moderate or complex disease who may tolerate AF poorly. Class I antiarrhythmic drugs must be avoided in patients with ACHD with CAD or significant subpulmonary or systemic ventricular dysfunction.<sup>14–16</sup> Amiodarone is an effective antiarrhythmic agent for maintaining sinus rhythm in patients with ACHD; however, long-term therapy is limited by adverse effects, particularly amiodarone-induced thyrotoxicosis, which is common in women with CHD, cyanotic CHD, and those with Fontan physiology.<sup>17</sup> Amiodarone should also be avoided in patients with ACHD who have a BMI <21 kg/m<sup>2</sup> due to the increased incidence of thyrotoxicosis in these patients.<sup>18</sup> Dofetilide may be a viable alternative to amiodarone in this complex population.<sup>19</sup> Extrapolating data from noncongenital populations, dronedarone is best avoided in patients with ACHD who have moderate or complex disease or significant ventricular dysfunction due to the increased risk of HF, stroke, and death.<sup>20,21</sup>
- Data on ablative strategies for AF in patients with ACHD are limited; however, when performed by experienced centers, AF ablation in patients with simple forms of CHD is safe.<sup>4,13</sup> Knowledge of the underlying congenital anatomy is key, as access to the atrial chambers may require different approaches, including transseptal puncture. Patients with ACHD who have persistent AF have lower success rates for ablation, and multiple procedures may be required.<sup>22</sup> There are insufficient data on the role, safety, and benefit of AF ablation in complex forms of CHD.
- PVI has a lower success rate in patients with ACHD than in patients with structurally normal hearts. The operator should understand the variations in systemic and pulmonary venous anatomy, such as a left superior vena cava, which may be a trigger for AF.<sup>9</sup> Due to related pathology in the right atrium of patients with repaired complex ACHD, additional ablative therapies directed at atriotomy scars and the CTI may be necessary. Cryoballoon ablation is a safe option for patients with simple or moderate forms of CHD and AF.<sup>23,24</sup>
- All patients with CHD should be considered for some form of thromboembolic prophylaxis. Select groups of patients with CHD are at higher risks for thromboembolic events, such as cyanotic lesions, those with low-flow states (Fontan physiology), and those with blind-ending cardiac chambers. The prevalence of cerebrovascular accidents in patients with ACHD is estimated to be 10- to 100-fold higher than age-matched controls, and thromboembolic events account for at least 4% of all-cause mortality in patients with CHD.<sup>25</sup> Increased complexity of CHD is associated with thromboembolic events, but CHA<sub>2</sub>DS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASC scores are not predictive of thromboembolic risk in patients with ACHD; therefore, therapies must be individualized.<sup>10</sup> Limited data are available for the use of DOACs in patients with ACHD, but in a survey, they appeared to be safe and effective.<sup>26</sup>

## 10.9. Prevention and Treatment of AF After Cardiac Surgery

### 10.9.1. Prevention of AF After Cardiac Surgery

Recommendations for Prevention of AF After Cardiac Surgery Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
2a	B-R	1. In patients undergoing cardiac surgery who are at high risk for postoperative AF, it is reasonable to administer short-term prophylactic beta blockers or amiodarone to reduce the incidence of postoperative AF. <sup>1-5</sup>
2a	B-R	2. In patients undergoing CABG, aortic valve, or ascending aortic aneurysm operations, it is reasonable to perform concomitant posterior left pericardiectomy to reduce the incidence of postoperative AF. <sup>6,7</sup>

#### Synopsis

New-onset AF after cardiac surgery is common and has been associated with increased risks of late mortality and stroke.<sup>8</sup> Trials of prophylactic amiodarone and beta blockers have demonstrated effectiveness reducing the occurrence of new AF, but not in all studies. Building off previous studies, the PALACS (Effect of Posterior Pericardiectomy on the Incidence of Atrial Fibrillation After Cardiac Surgery) randomized trial studied the use of posterior left pericardiectomy<sup>7</sup> and found significant reduction of AF in the treated group (17% versus 32% no intervention group;  $P=0.0007$ ; OR, 0.44). Colchicine has shown uncertain benefit based on the results of more recent studies compared with earlier encouraging trials. Drug adverse effects result in frequent drug discontinuation.<sup>9-11</sup>

#### Recommendation-Specific Supportive Text

1. Preoperative prophylaxis with beta blockers or amiodarone has shown mixed benefit, and studies are difficult to compare because of variable medication combinations.<sup>1-5</sup> One double-blind RCT of 601 patients listed for nonemergency CABG surgery and/or valve replacement/repair surgery showed a significant reduction of AF with amiodarone.

2. A meta-analysis and RCT showed that the incidence of postoperative AF was significantly lower in patients treated with posterior left pericardiectomy during their cardiac procedure; however, the studies did not include patients undergoing mitral or tricuspid procedures.<sup>6,7</sup>

### 10.9.2. Treatment of AF After Cardiac Surgery

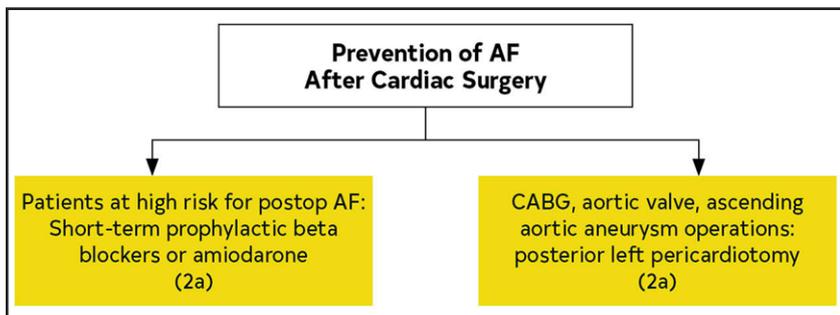
Recommendations for Treatment of AF After Cardiac Surgery Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	A*	1. In postoperative cardiac surgery patients, beta blockers* are recommended to achieve rate control for AF <sup>1-4</sup> unless contraindicated or ineffective in which case a nondihydropyridine calcium channel blocker† is recommended. <sup>5</sup>
	B-R†	
1	B-R	2. In hemodynamically stable cardiac surgery patients with postoperative AF, rate-control (target heart rate, <100 bpm) and/or rhythm-control medications are recommended as initial therapy, with the choice of strategy according to patient symptoms, hemodynamic consequences of the arrhythmia, and physician preference. <sup>5,6</sup>
1	B-R	3. In patients who develop poorly tolerated AF after cardiac surgery, direct current cardioversion in combination with antiarrhythmic drug therapy is recommended, with consideration of imaging to rule out left appendage thrombus before cardioversion in those patients in whom AF has been present >48 hours and who have not been on anticoagulation. <sup>5,6</sup>
2a	B-NR	4. In patients who develop postoperative AF after cardiac surgery, it is reasonable to administer anticoagulation when deemed safe in regard to surgical bleeding for 60 days after surgery unless complications develop and to reevaluate the need for longer term anticoagulation at that time. <sup>5,7</sup>
2a	C-LD	5. In patients who develop AF after cardiac surgery and who are treated with rate-control strategy, at 30- to 60-day follow-up it is reasonable to perform rhythm assessment and, if AF does not revert to sinus rhythm spontaneously, consider cardioversion after an adequate duration of anticoagulation. <sup>5,6</sup>

\*A LOE applies to the data on beta blockers.

†B-R LOE applies to the data on nondihydropyridine calcium channel blockers.

#### Synopsis

For new-onset AF after cardiac surgery, rate control is typically managed with beta blockers, or calcium channel



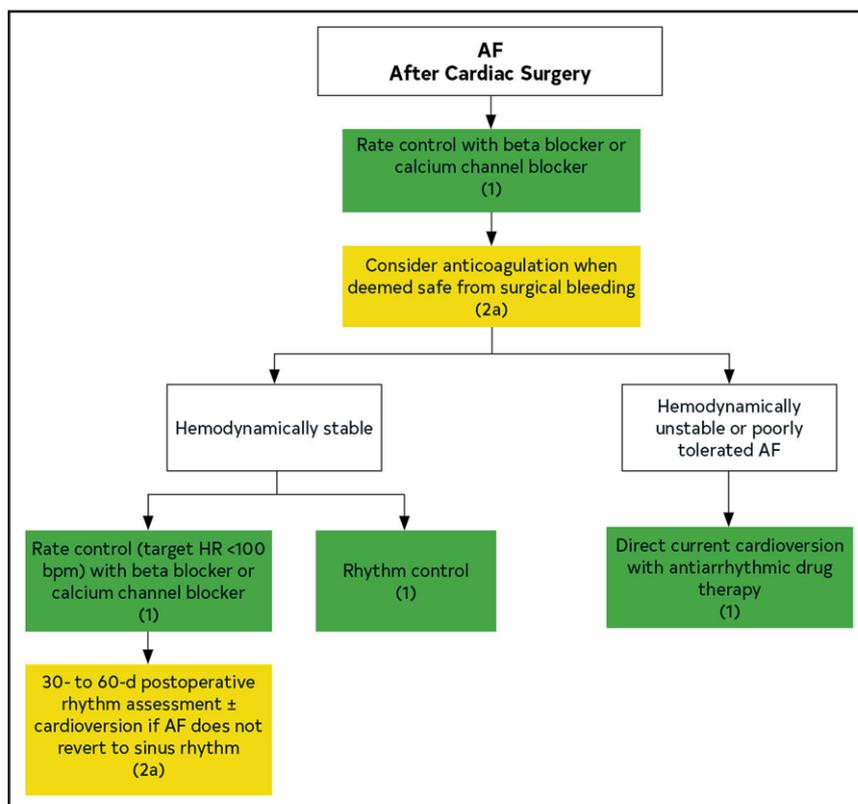
**Figure 25. Prevention of AF After Cardiac Surgery.**

Colors correspond to Table 2. AF indicates atrial fibrillation; and CABG, coronary artery bypass graft.

blockers.<sup>1-4</sup> A randomized trial showed no significant clinical differences comparing a strategy of rate-control versus rhythm-control medications for patients who are hemodynamically stable.<sup>5</sup> For those with poorly controlled AF, cardioversion is reasonable, but for those with >48 hours of AF, imaging of the LAA (even if surgically closed) should be considered.<sup>5,6</sup> The use of cardioversion and imaging in postoperative patients is a judgment call considering the patient's clinical condition. For patients who develop postoperative AF, including during follow-up postdischarge, rhythm assessment, and possible cardioversion for the small number who are still in AF, should be considered.<sup>5,6</sup> Colchicine had been shown to be effective, but more recent studies did not confirm this, and gastrointestinal adverse effects may be significant.<sup>8-10</sup>

### Recommendation-Specific Supportive Text

1. The use of beta blockers to control heart rate is well documented.<sup>1-4</sup> Calcium channel blockers are an option for rate control when beta blockers are ineffective.<sup>5</sup>
2. The use of rate control or rhythm control are both acceptable options in hemodynamically stable patients because neither has a distinct clinical advantage over the other based on a randomized study that included 529 patients. In this study, patients in the rhythm-control group received amiodarone.<sup>5,6</sup>
3. Cardioversion of patients with sustained postoperative AF is regularly performed, especially for those patients with hemodynamically poorly tolerated AF. Cardioversion is routinely combined with pharmacological therapy, especially amiodarone.<sup>5,6</sup>
4. A review of 8 observational studies that included 15 335 patients found a protective impact on the mortality rate at 5 years but no differences in thromboembolic events in patients with postoperative AF treated with anticoagulants.<sup>7</sup> In general, the duration of anticoagulation is a minimum of 60 days; in the randomized trial of rate control versus rhythm control, if patients remained in AF or had recurrent AF 48 hours after randomization, anticoagulation was recommended to be continued for 60 days, unless complications occurred. Patients should be evaluated before discontinuation to determine underlying rhythm, especially those at high risk for stroke.
5. The need for a rhythm-control strategy should be evaluated postdischarge. Patients who tolerate rate control can be followed and often convert spontaneously after 6 to 8 weeks. A net advantage of rate control is earlier discharge in hemodynamically stable patients. Those who do not convert can be managed accordingly with rhythm-control strategy.<sup>5,6</sup>



**Figure 26. Treatment of AF After Cardiac Surgery.**

Colors correspond to Table 2. AF indicates atrial fibrillation; and HR, heart rate.

## 10.10. Acute Medical Illness or Surgery (Including AF in Critical Care)

Recommendations for Acute Medical Illness or Surgery (Including AF in Critical Care)		
Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
1	B-NR	1. Patients with AF who are identified in the setting of acute medical illness or surgery should be counseled about the significant risk of recurrent AF after the acute illness is resolved. <sup>1-6</sup>
2a	B-NR	2. In patients with AF who are identified in the setting of acute medical illness or surgery, outpatient follow-up for thromboembolic risk stratification and decision-making on OAC initiation or continuation, as well as AF surveillance, can be beneficial given a high risk of AF recurrence. <sup>4-9</sup>
2b	B-NR	3. In patients with AF who are identified in the setting of critical illness due to sepsis, the benefits of anticoagulation during critical illness for stroke prevention are uncertain. <sup>10,11</sup>

### Synopsis

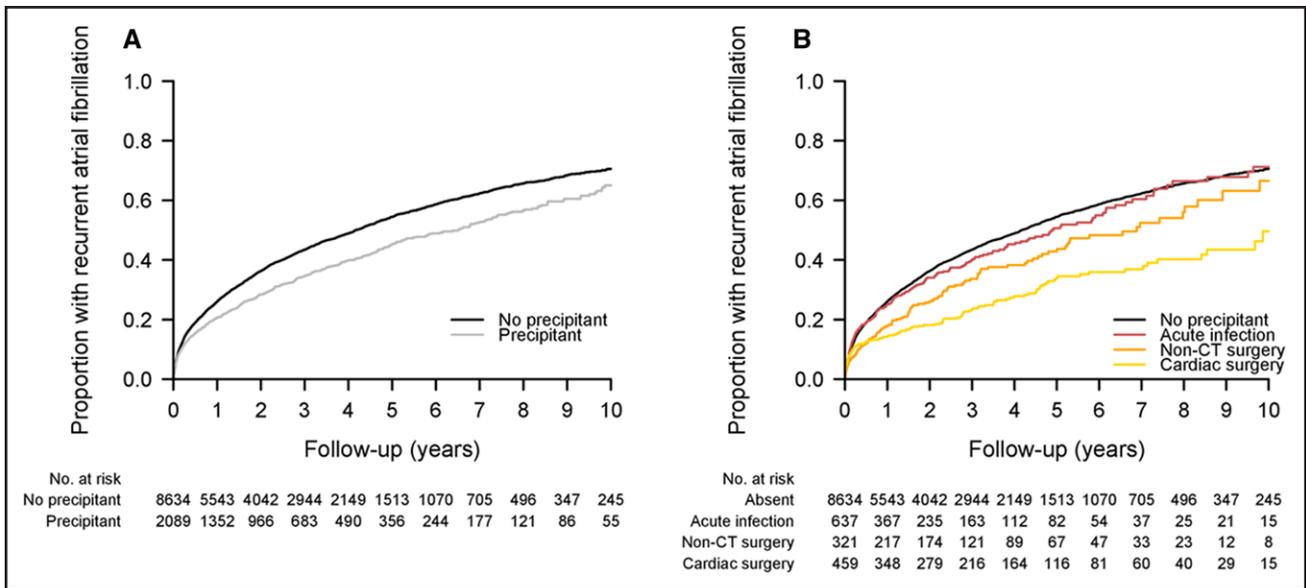
AF identified in the setting of hospitalization for acute noncardiac illness (acute AF), including patients who are critically ill, may represent new-onset AF that has been detected and treated for the first time. Incidence ranges from 1% to 46% in medical illness,<sup>1,12-14</sup> with 6% to 22% in severe sepsis,<sup>15</sup> and 3% to 16% after noncardiac surgery.<sup>16</sup> AF can be an incidental finding during low-risk procedures but can occur associated with a range of conditions, including critical illness or sepsis. A combination of underlying arrhythmogenic substrate and triggers related to the acute illness likely contribute to acute AF. Acute AF can be paroxysmal or persistent, with or without symptoms, and is associated with higher risk of AF recurrence.<sup>1-3</sup> Acute AF is also associated with prolonged hospitalization<sup>13,14</sup> as well as increased morbidity<sup>12,15</sup> and mortality.<sup>13,15</sup> Management of acute AF is directed toward detection and treatment of potential triggers, optimizing hemodynamics, rate and/or rhythm control, and reducing in-hospital and long-term risk of stroke. Rate- or rhythm-control strategy should be individualized, balancing the impact of rapid rates and atrioventricular dyssynchrony on hemodynamics with ability to tolerate treatment. Decisions regarding initiating anticoagulation should be based on risk stratification of patient substrate and comorbidities, and the timing should take into consideration bleeding risks and the complexity of the acute illness.

### Recommendation-Specific Supportive Text

1. In patients who develop or are discovered to have AF in the setting of acute medical illness and noncardiac surgery, recurrent AF was noted in 42% to 68%<sup>1,2</sup> and 39%,<sup>3</sup> respectively, during 5-year follow-up. Regardless of presence of an

initial precipitant, recurrent AF was associated with increased risks of HF (HR, 2.74 [95% CI, 2.39-3.15];  $P < 0.001$ ), stroke (HR, 1.57 [95% CI, 1.30-1.90];  $P < 0.001$ ), and mortality (HR, 2.96 [95% CI, 2.70-3.24];  $P < 0.001$ ).<sup>2</sup>

2. In 10723 patients with newly diagnosed AF (67.9±9.9 years, 41% women) identified from a longitudinal database, 19% of patients had an acute AF precipitant, the most common being cardiac surgery (22%), pneumonia (20%), and noncardiac surgery (15%). AF recurrence at 5 years was 41% among those with a precipitant versus 52% in those without one (adjusted HR, 0.75 [95% CI, 0.69-0.81];  $P < 0.001$ ) (Figure 27).<sup>3</sup> Regardless of a precipitant, recurrent AF was associated with increased risk of HF (HR, 2.74 [95% CI, 2.39-3.15];  $P < 0.001$ ), stroke (HR, 1.57 [95% CI, 1.30-1.90];  $P < 0.001$ ), and death (HR, 2.96 [95% CI, 2.70-3.24];  $P < 0.001$ ). In patients with acute AF after cardiac surgery, observational studies show that those who underwent continuous rhythm monitoring had a higher detection of AF.<sup>4-6</sup> No randomized clinical trial has specifically compared different monitoring strategies for outpatient follow-up of patients with acute AF. However, parallels could be drawn from studies like the CRYSTAL-AF<sup>8</sup> and SEARCH-AF (Post-Surgical Enhanced Monitoring for Cardiac Arrhythmias and Atrial Fibrillation)<sup>9</sup> trials, which showed increased sensitivity for AF detection with long-term monitoring. Close outpatient follow-up with consideration of heart rhythm monitoring and thromboembolic risk stratification is important considering the high risk of AF recurrence in these patients, especially in those who underwent noncardiac surgery and with risk factors for stroke in whom the AF is likely to recur (Figure 28). The optimal frequency, duration, and type of rhythm monitoring for patients with acute AF remain unclear and need further study.
3. In a retrospective cohort study of 38582 patients with AF and sepsis admitted to US hospitals from July 1, 2010, to June 30, 2013, 13611 patients (35.3%) received parenteral anticoagulation for AF. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score was a poor predictor of acute stroke risk, and parenteral anticoagulation did not reduce stroke risk (1.3% versus 1.4%; RR, 0.94 [95% CI, 0.77-1.15]) and was associated with an increased risk of clinically significant bleeding (8.6% versus 7.2%; RR, 1.21 [95% CI, 1.10-1.32]). Risk of stroke did not differ whether patients had preexisting AF and new onset AF.<sup>10</sup> In a retrospective cohort study of 102 patients ≥65 years of age who were hospitalized with sepsis and with new-onset AF, 28% received

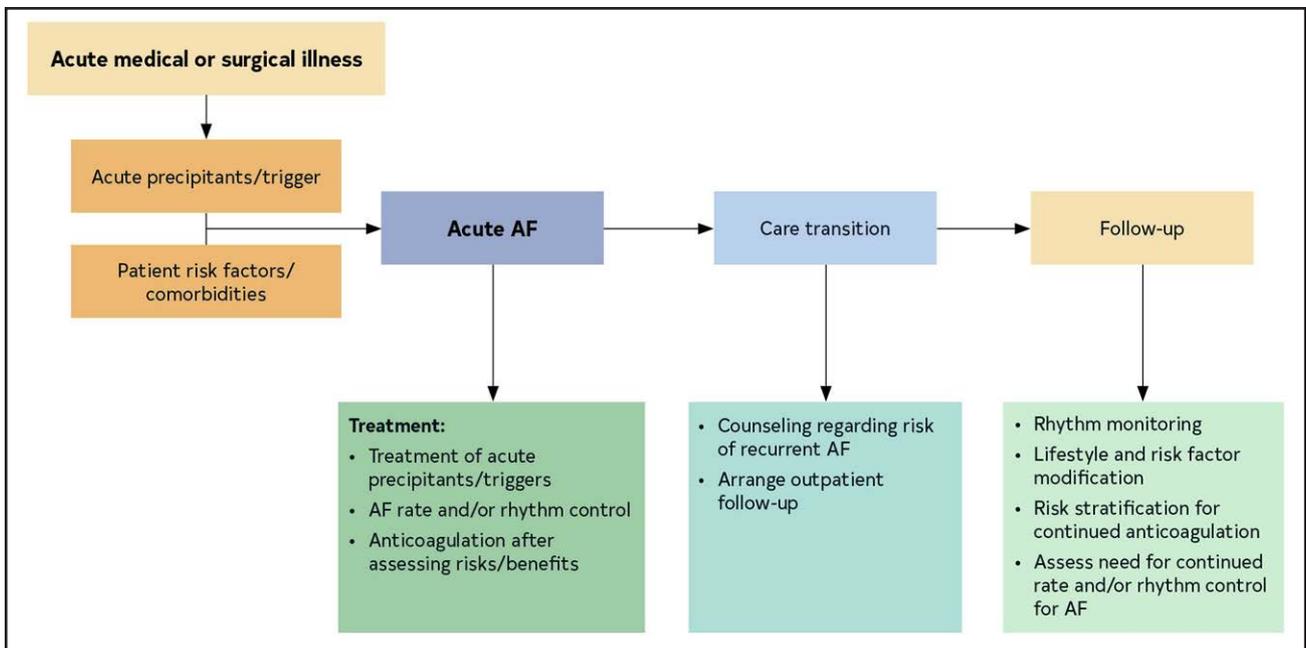


**Figure 27. Unadjusted Cumulative Risk of AF Recurrence.**

Unadjusted curves displaying cumulative risk of recurrent AF, generated using Kaplan-Meier method. (A) Overall risk of recurrent AF among individuals with and without acute precipitants. (B) Overall risk of recurrent AF among individuals with infection, cardiac surgery, and noncardiothoracic surgery compared with no precipitant. These 3 precipitants were selected for display because the risk of recurrent AF was significantly lower compared with the referent group without precipitants in multivariable adjusted models. Individuals with other AF precipitants were excluded from this plot for clarity. Reproduced with permission from Wang et al.<sup>3</sup> Copyright 2020 American Heart Association, Inc. AF indicates atrial fibrillation; and CT, cardiothoracic.

a prescription for OACs within 30 days of admission. Over 3-year follow-up, no significant association was noted between anticoagulation and a lower incidence of ischemic stroke (OR, 1.98 [95% CI, 0.29-13.47]) or bleeding (OR, 0.96

[95% CI, 0.29-3.21]).<sup>11</sup> Gaps in knowledge exist, and further research is needed to better understand the benefits and risks of acute and long-term anticoagulation in critically ill patients with acute AF.



**Figure 28. Acute Medical or Surgical Illness.**

Adapted with permission from Chyou et al.<sup>17</sup> Copyright 2023 American Heart Association, Inc. AF indicates atrial fibrillation.

## 10.11. Hyperthyroidism

Recommendation for Hyperthyroidism Referenced studies that support the recommendation are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendation
1	B-NR	1. In patients with hyperthyroidism and AF who have an elevated risk of stroke based on a standard clinical risk score, anticoagulation is recommended until thyroid function has returned to normal and sinus rhythm can be maintained. <sup>1,2</sup>

### Synopsis

Hyperthyroidism, defined as elevated blood levels of thyroid hormone with reduced levels of thyroid-stimulating hormone, is relatively common and may not lead to overt symptoms of thyrotoxicosis.<sup>3,4</sup> Patients with hyperthyroidism are at increased risk of developing AF,<sup>5</sup> which resolves in most cases after the restoration of the euthyroid state with effective antithyroid treatment.<sup>6,7</sup> Excess thyroid hormone increases sensitivity to catecholamines,<sup>3,8</sup> and beta blockers reduce symptoms and tachycardia in patients with hyperthyroidism.<sup>9–12</sup> Nonselective beta blockers may reduce the systemic symptoms of hyperthyroidism a bit more than beta-1–selective agents do, and propranolol reduces the peripheral conversion of T4 to T3.<sup>10,13</sup> Although it is uncertain whether hyperthyroidism is an independent risk factor for stroke, many patients have other risk factors that elevate stroke risk, and anticoagulation reduces risk of stroke to a similar extent among patients with and without hyperthyroidism.<sup>1,2,14</sup> Restoration of sinus rhythm is unlikely until a euthyroid state has been achieved<sup>15</sup> and, in 1 study, spontaneous reversion to sinus rhythm occurred at a median of 1 to 3 weeks after thyroid hormone levels returned to normal.<sup>6</sup>

### Recommendation-Specific Supportive Text

1. Patients with hyperthyroidism often have laboratory findings that suggest hypercoagulability,<sup>16</sup> but it is uncertain whether this translates into a higher risk of stroke.<sup>1,17</sup> Nevertheless, patients with hyperthyroidism are commonly at elevated risk of stroke due to other clinical factors, so anticoagulation should be considered using the framework in **Section 6.3.1 (“Antithrombotic Therapy”)**. A Danish national registry study found that patients with thyrotoxicosis and AF had a lower overall risk of thromboembolic events but a similar reduction in the risk of thromboembolic events from anticoagulation compared with patients who did not have a secondary cause of AF.<sup>5</sup> In a large, randomized trial of apixaban versus warfarin, patients with a history of hyperthyroidism or hypothyroidism had risk of stroke similar to that of patients with no history of thyroid disease, and the effectiveness of apixaban in reducing stroke was consistent across subgroups with and without a history of thyroid disease.<sup>16</sup>

## 10.12. Pulmonary Disease

Recommendations for Pulmonary Disease Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
2a	B-R	1. In patients with AF and COPD, it is reasonable to use cardioselective beta blockers for rate control of AF, especially where other indications exist (eg, MI and HF). <sup>1–3</sup>
2a	B-NR	2. In patients with pulmonary hypertension (PH) with pulmonary vascular disease and AF or AFL, a rhythm-control strategy is reasonable to improve functional status and potentially prolong survival. <sup>4–12</sup>

### Synopsis

Pulmonary disease is commonly associated with arrhythmias. AF is common in COPD and is associated with an increased risk of mortality and bleeding.<sup>13</sup> The combination of AF and asthma is less common, and beta blockers are generally avoided to prevent bronchospasm. A bidirectional relationship is seen between AF and pulmonary embolus (PE), although it is little studied. The risk of PE is increased in patients with AF.<sup>14</sup> AF may also complicate acute PE, where it is a marker of increased risk of mortality.<sup>15</sup> Whether AF in the setting of PE should influence the intensity or duration of anticoagulation, or is associated with future AF recurrence, is unknown. AF and other supraventricular arrhythmias are important causes of decompensation in patients with PH, which is especially well described in World Health Organization groups 1 and 4. A successful rhythm-control strategy is associated with better outcomes in these patients.

### Recommendation-Specific Supportive Text

1. AF is common in patients with COPD, with a prevalence of 11% in a large European registry.<sup>16</sup> Furthermore, patients with COPD often have other concomitant heart disease. Because beta-2 agonists can be used for the treatment of COPD, there has been a reluctance to prescribe beta blockers in case these would antagonize beta-2 agonists or precipitate bronchospasm.<sup>17</sup> However, a systematic review and meta-analysis of observational studies found that beta-blocker use, for diverse indications including HF and CAD, was associated with a significantly reduced risk of mortality in patients with COPD.<sup>1</sup> Another meta-analysis of RCTs assessing the effect of cardioselective beta blockers on respiratory function and symptoms did not find any change in these parameters or in response to beta-2 agonists.<sup>2</sup> An RCT of patients with advanced COPD at risk of severe exacerbation, but without an indication for beta-blocker treatment, found no difference in the time to first exacerbation but did find an increased risk of severe exacerbation.<sup>3</sup> Therefore, although other agents can be used for rate control of AF (**Section 7, “Rate Control”**), beta blockers,

especially cardioselective beta blockers, for treatment of AF need not be avoided when indicated, especially in patients with less than severe COPD. However, beta blockers can exacerbate reactive airway disease and are generally avoided in that setting, such as in patients with asthma.

2. Atrial arrhythmias are common in PH with pulmonary vascular disease (PH<sub>PVD</sub>; hemodynamically defined as PH with increased pulmonary vascular resistance and normal left heart filling pressures, typical of World Health Organization group 1 but also of groups 3 and 4). Right atrial contraction accounts for a significantly greater proportion of total right heart function in patients with PH<sub>PVD</sub> than in normal subjects,<sup>18</sup> and the onset of atrial arrhythmia is frequently associated with clinical deterioration.<sup>4-12</sup> Restoration of sinus rhythm results in improvement, whereas persistent arrhythmia or recurrence is associated with mortality.<sup>4,8,9</sup> Pharmacological rhythm control and cardioversion have both been used, although negative inotropy may limit antiarrhythmic drug therapy. Catheter ablation of typical AFL has been well described in patients with PH<sub>PVD</sub> with acceptable results and safety, as well as improvement in clinical and hemodynamic parameters.<sup>5,7,12</sup> LA ablation has also been described, although the possibility of creating a right-to-left shunt should always be considered when planning transeptal puncture. Anesthetic management is also complex, and these patients are best cared for by centers with extensive clinical expertise in these conditions.

### 10.13. Pregnancy

Recommendations for Pregnancy Referenced studies that support the recommendations are summarized in the Online Data Supplement.		
COR	LOE	Recommendations
1	B-NR	1. In pregnant patients with AF, DCCV is safe to the patient and fetus and should be performed in the same manner as in patients who are not pregnant. <sup>1</sup>
2b	C-LD	2. In pregnant individuals with structurally normal hearts and hemodynamically stable AF, pharmacological cardioversion with agents with history of safe use in pregnancy, such as intravenous procainamide, may be considered. <sup>1,2</sup>
2a	C-LD	3. In pregnant individuals with AF and without structural heart disease, antiarrhythmic agents with history of safe use in pregnancy (eg, flecainide and sotalol) are reasonable for maintenance of sinus rhythm. <sup>1,2</sup>
2a	B-NR	4. In pregnant individuals with persistent AF, rate-control agents with a record of safety in pregnancy, such as beta blockers (eg, propranolol or metoprolol) and digoxin, either alone or in combination with beta blockers, are reasonable as first-line agents. <sup>1,2</sup>
2b	C-LD	5. Pregnant individuals with AF and elevated risk of stroke may be considered for anticoagulation with the recognition that no anticoagulation strategy is completely safe for both the mother and fetus, and an SDM discussion should take place regarding risks to both mother and fetus (Table 28). <sup>3</sup>

### Synopsis

The incidence of atrial arrhythmias is rising in pregnancy, and data from the national inpatient sample suggest that this is largely driven by increasing incidence of AF, with a reported frequency of 27 per 100 000 hospitalizations.<sup>4</sup> The incidence of AF/AFL in pregnant patients with heart disease is 1.3%, with a peak occurrence between 23 and 30 weeks gestation.<sup>5,6</sup> Hospitalizations during pregnancy for arrhythmias are associated with an increased risk of maternal and fetal adverse outcomes. AF during pregnancy is associated with increased maternal mortality (OR, 13.13 [95% CI, 7.77-22.21]; *P*<0.0001).<sup>9</sup>

Atrial arrhythmias may manifest for the first time during pregnancy; however, AF is usually associated with underlying structural or CHD. Factors associated with an increased incidence of AF in pregnant individuals include advanced maternal age,<sup>6</sup> African American race, lower socioeconomic status, and left-sided obstructive lesions.<sup>4,5</sup> Obesity is associated with the development of hypertensive disorders of pregnancy, which is also a known risk factor for AF.<sup>7</sup> Another potential mechanism for development of AF in pregnancy is the cardiogastric interaction that occurs with elevated progesterone levels, leading to gastroesophageal reflux disease.<sup>8</sup>

In patients deemed to be at high risk of stroke, recommendations for anticoagulation in pregnancy are extrapolated from experience in managing VHD. DOACs are contraindicated during pregnancy and during breastfeeding because of a lack of data to support their safety and efficacy in this patient population.

### Recommendation-Specific Supportive Text

1. Rapid atrioventricular conduction may have serious hemodynamic consequences for both mother and fetus.<sup>9</sup> DCCV of AF in pregnant individuals is safe for both mother and fetus and should be performed within 48 hours of presentation to minimize risk of stroke.<sup>1</sup> Appropriate sedation should be provided to the pregnant individuals before DCCV. Fetal monitoring is generally used during and directly after DCCV.
2. Antiarrhythmic drugs are used in pregnancy for both maternal and fetal conditions; therefore, their mechanisms and adverse effect profile must be tolerable to both mother and fetus. These medications should be avoided if possible during the first trimester, and initiation of the drug should be attempted at the lowest dose with involvement of an electrophysiologist or cardiologist skilled in the management of arrhythmias in pregnancy.<sup>10</sup> Intravenous ibutilide has been used effectively in pregnant women with refractory AF, although published reports included a very small number of patients. In a pregnant patient presenting with AF and manifest preexcitation, intravenous procainamide is also an option.<sup>11</sup>
3. In pregnant individuals with structurally normal hearts and AF, rhythm-control strategies may include

**Table 28. Anticoagulation Strategies During Pregnancy**

Antenatal Options				
	Method 1	Method 2	Method 3	Alternative Method 4
First trimester	Warfarin ≤5 mg	LMWH	UFH	LMWH
Second trimester	Warfarin	Warfarin	Warfarin	LMWH
Third trimester	Warfarin	Warfarin	Warfarin	LMWH
Delivery Planning				
	Method 1	Method 2		
1 wk before	Discontinue warfarin → continuous IV UFH	Dose-adjusted LMWH		
36 h before	Continuous IV UFH	Switch to continuous IV UFH		
4-6 h before	Stop IV heparin	Stop IV heparin		

Adapted with permission from Otto et al.<sup>15</sup> Copyright 2021 American Heart Association, Inc., and American College of Cardiology Foundation.

IV indicates intravenous; LMWH, low-molecular-weight heparin; and UFH, unfractionated heparin.

agents with a long record of safety (eg, flecainide and sotalol) with appropriate monitoring that includes surveillance ECGs.<sup>1,12</sup> Amiodarone is generally avoided and reserved for life-threatening arrhythmias because of potential toxicities to the fetus, including goiter, neurodevelopmental abnormalities, bradycardia, delayed growth, and premature birth.<sup>10,12</sup>

- In pregnant individuals with persistent AF, rate-control strategies may include beta blockers with long record of safety in pregnancy (propranolol, metoprolol) or digoxin. Atenolol is generally avoided in pregnancy due to concerns about intrauterine growth retardation. Serum digoxin levels may be unreliable in pregnancy as digoxin-like immunoreactive substances are increased in pregnant individuals and react with antibodies against digoxin, interfering with the radioassay used for detection of digoxin serum levels.<sup>13</sup>
- Tools available to predict stroke risk in AF have not been validated in pregnancy. In the rare case of AF with no risk factors or signs of heart disease, anticoagulation may not be necessary.<sup>1,14</sup> SDM should be used when considering anticoagulation during pregnancy (Table 28). Some patients may be deemed at high risk for stroke, such as those with mitral stenosis, for which recommendations for anticoagulation in pregnancy are extrapolated from experience in managing VHD. Warfarin may be administered in the first trimester providing the dose needed to achieve a therapeutic INR is ≤5 mg. If the dose of warfarin is >5 mg/day, low-molecular-weight heparin should be administered throughout the first trimester and then transitioned to warfarin for the remainder of the antenatal period until 36 hours before a planned delivery, at which time unfractionated heparin is

started.<sup>15</sup> Vaginal delivery should be advised for most women, and VKAs are generally held to mitigate risk of bleeding complications.<sup>13</sup> Use of novel DOACs is not recommended during pregnancy in view of lack of evidence about safety.<sup>16</sup>

## 10.14. Cardio-Oncology and Anticoagulation Considerations

### Recommendations for Cardio-Oncology and Anticoagulation Considerations

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

COR	LOE	Recommendations
1	C-LD	1. In patients with cancer and AF, multidisciplinary communication including cardiology, oncology and other clinicians, and SDM with the patient is recommended to optimize cancer and AF treatment and to reduce the risk of drug-drug interactions, QTc prolongation, proarrhythmia, bleeding, and thromboembolism. <sup>1-3</sup>
2a	C-LD	2. In patients who are to be initiated on cancer therapies associated with an increased risk of developing AF, increased vigilance for incident AF and treatment of contributing factors is reasonable to decrease morbidity. <sup>1,4-6</sup>
2a	B-NR	3. In most patients with AF and cancer (remote history or receiving active cancer treatment), DOACs are reasonable to choose over VKAs for stroke risk reduction. <sup>7b</sup>

### Synopsis

Patients with cancer have an increased risk of AF. A Danish nationwide study observed an incident AF rate of 17.4 per 1000 person-years compared with 3.7 per 1000 person-years in patients without cancer.<sup>9</sup> A meta-analysis of observational studies demonstrated the risk of AF to be ~47% higher in patients with cancer compared with patients without cancer.<sup>5,10</sup> The increased risk of AF is likely related to increased age, shared risk factors between cancer and CVD (eg, obesity and systemic inflammation), coexistent comorbidities (eg, hypertension and HF), cardiac involvement by the tumor, as well as certain medical therapeutics (Table 29), oncologic surgery, especially thoracic, and thoracic radiation therapy.<sup>11,12</sup> New-onset AF in patients with cancer is associated with a higher risk of HF, thromboembolism, bleeding, and mortality.<sup>13-15</sup> Notably, Bruton's tyrosine kinase (BTK) inhibitors, such as ibrutinib, which are used to treat chronic lymphocytic leukemia and lymphoproliferative malignancies and often used for an extended period of time, are associated with a higher risk of AF due to off-target cardiac effects.<sup>16</sup> In 1 meta-analysis, the risk of AF with use of ibrutinib was 4 times higher compared with that without use of ibrutinib.<sup>17</sup>

Although patients with cancer are underrepresented in the major trials comparing DOACs to VKAs, large observational studies and meta-analyses of studies of patients with cancer and AF have demonstrated similar or lower rates of ischemic stroke and bleeding in patients taking DOACs compared with warfarin.<sup>7b</sup> Patients with

**Table 29. Medical Cancer Therapy Associated With Increased Risk of AF (>1%)**

Cancer Therapy	Frequency Reported in Clinical Trials and Observational Studies		Comments
	Common: Incidence 1%-10%	Frequent: >10%	
<b>Anthracyclines</b> Doxorubicin, epirubicin, idarubicin, mitoxantrone		X	AF may be a secondary result of anthracycline cardiotoxicity; studies in different populations demonstrate variable risk of AF
<b>Antimetabolites</b> Clofarabine combined with cytarabine 5FU Cepecitabine Gemcitabine	X X X	X	
<b>Alkylating agents</b> Cyclophosphamide Melphalan + stem cell transplantation	X	X*	*Stem cell transplantation is associated with an increased risk of AF, <sup>28,29</sup> and the risk may be higher with melphalan-associated regimens.
<b>Immunomodulatory drugs</b> Lenalidomide Interleukin-2	X X		Given rates reported from patients with multiple myeloma, AF due to underlying cardiac AL amyloid may contribute
<b>TKIs</b> Ibrutinib (BTKi) Acalbrutinib (second-generation BTKi) Zanubrutinib (second-generation BTKi) Ponatinib (BCR-ABL TKI) and other TKIs (eg, trametinib, osimertinib, nilotinib, ribociclib) <b>VEGF inhibitor</b> Sorafenib in combination with 5FU <b>BRAF inhibitor</b> Vemurafenib	X† X X X X X X	X†	†Reported AF rates with ibrutinib have varied across trials (4%-18%), <sup>6,30</sup> partly related to varying duration of follow-up and patient factors. Second-generation BTKis have more selective BTK activity and are associated with a lower incidence of AF than ibrutinib. <sup>31</sup> Based on FDA adverse event reporting system <sup>4</sup>
<b>CAR T-cell therapy</b> Tisagenlecleucel Axicabtagene ciloleucel	X X		
<b>Monoclonal antibodies</b> Rituximab	X		

Table developed by 2023 Atrial Fibrillation Guideline Writing Committee. Data extracted from Buza et al<sup>32</sup> and Fradley et al<sup>33</sup>

AF indicates atrial fibrillation; BTKi, Bruton's kinase inhibitor; CAR, chimeric antigen receptor; FDA, US Food and Drug Administration; 5FU, 5 fluorouracil; and TKI, tyrosine kinase inhibitor.

AF and cancer are at an increased risk for major bleeding.<sup>18</sup> They also are commonly on antineoplastic agents, which may have important drug interactions with OACs.<sup>19</sup> Thus, these factors should be carefully considered in determining indication and choice of OAC.

**Recommendation-Specific Supportive Text**

1. In patients with cancer who develop AF in the presence of cancer therapeutics associated with an increased risk of incident AF (Table 29), the first approach usually consists of optimizing AF control while continuing cancer therapy. However, if AF control cannot be achieved, decisions regarding dose reduction of the cancer therapy or even stoppage can only be made in concert with the oncology team and SDM with the patient. Drug-drug interactions between cancer, antiarrhythmic, rate-control, and anticoagulant therapies are common and require close attention.<sup>1</sup> For example, in the case of BTK inhibitors, CYP3A inhibitors such as amiodarone, dronedarone, verapamil, and diltiazem are usually avoided, due to the associated risk of elevation in ibrutinib levels.<sup>1</sup> Further, ibrutinib can raise levels of digoxin, a P-glycoprotein substrate.<sup>1</sup> Therefore, beta blockers are considered the best

option for rate control in BTK inhibitor-associated AF. If additional agents are needed for AF control, any concomitant reduction in dose of ibrutinib is guided by oncology.<sup>1</sup> Further, QTc prolongation, which is more common in patients with cancer due to several cancer therapies, antiemetics, antibiotics, and electrolyte derangements, can be further exacerbated by QT-prolonging antiarrhythmic agents.<sup>3</sup> Structured screening by pharmacists for potential drug-drug interactions could provide benefit.<sup>2</sup>

2. Certain medical cancer therapies can increase the risk of incident AF (Table 29). Patients with cancer and AF are older and have higher rates of hypertension, MI, and HF compared with those who do not develop AF.<sup>13-15</sup> The development of perioperative AF has been strongly associated with perioperative complications.<sup>20</sup> In general, patients with cancer and CVD may be undertreated with GDMT or less often referred to specialists for cardiovascular care.<sup>21</sup> Optimization of cardiovascular conditions such as hypertension and HF may decrease the risk of incident AF, AF recurrence, and of major adverse cardiovascular events, including stroke.<sup>22-25</sup> Therefore, in patients without a history of AF, or those with previous history of AF, who are to be started on

cancer therapies associated with a higher risk of AF, evaluation and optimization of cardiovascular risk factors or disease by a cardiologist could be beneficial in decreasing incident and recurrent AF and associated cardiovascular events, although no data are available specifically in patients with cancer. Furthermore, elevated natriuretic peptides or a history of previous AF can identify patients at higher risk of AF after major thoracic cancer surgery.<sup>26,27</sup>

- No large RCTs are available that compare DOACs to warfarin in patients with AF and cancer. A meta-analysis of post-hoc analyses of RCTs and retrospective observational studies that compared DOACs with warfarin in patients with AF and cancer (n=229221) demonstrated a lower risk of stroke or systemic embolism (RR, 0.65 [95% CI, 0.52-0.81];  $P=0.001$ ) and major bleeding (RR, 0.68 [95% CI, 0.50-0.92];  $P=0.01$ ) with DOACs.<sup>8</sup> This meta-analysis included post hoc analyses of patients with cancer and AF from the ROCKET AF (rivaroxaban versus warfarin), ENGAGE TIMI-48 (edoxaban versus warfarin), and ARISTOTLE (apixaban versus warfarin) trials. These findings were consistent in patients defined as having active cancer, although definitions of active cancer varied by study. An additional large retrospective observation study comparing DOACs to warfarin in patients with active cancer demonstrated a lower risk of the composite endpoint of ischemic stroke/intracranial bleeding in patients taking DOACs compared with VKA (adjusted HR, 0.65 [95% CI, 0.48-0.88]).<sup>7</sup> Although most of the data in this patient population came from retrospective observational studies that may be prone to selection bias, findings are largely consistent with post hoc analyses from RCTs and the major RCTs comparing DOACs with VKA in general. Special consideration should be given to patient bleeding risk and antineoplastic drug interactions in this patient population (Table 30).<sup>18,19</sup>

### 10.15. CKD and Kidney Failure

CKD and kidney failure (formerly end-stage renal disease) share common risk factors with AF, such as hypertension and diabetes, and unsurprisingly, CKD and AF are associated in a disproportionate manner. In population studies, baseline serum creatinine, eGFR, and proteinuria were strongly associated with incident of AF during follow-up.<sup>1,2</sup> AF at baseline also predicted new renal dysfunction or proteinuria, suggesting a bidirectional relationship between CKD and AF.<sup>2</sup> In an insurance database of 206229 adults with confirmed CKD, over a mean follow-up of 5 years, there was a 67% increased rate of kidney failure among patients with CKD who developed incident AF compared with those without AF, even after adjustment for baseline factors.<sup>3</sup> Data on the management of AF in

**Table 30. Special Considerations for Anticoagulation in Patients With AF on Active Cancer Treatment**

Increased bleeding risk	High bleeding risk estimators (eg, HAS-BLED) Thrombocytopenia (platelet <50 000/uL) Intracranial malignancy Gastrointestinal malignancy History of major bleeding Severe kidney dysfunction (eGFR <30 mL/min/1.73 m <sup>2</sup> )
Drug interactions	P-glycoprotein inducers or inhibitors CYP3A4 inducers or inhibitors

AF indicates atrial fibrillation; eGFR, estimated glomerular filtration rate; and HAS-BLED, hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio (INR), elderly (age ≥65 years), drugs/alcohol concomitantly).

patients with CKD is limited because the major trials of rate control, rhythm control, and catheter ablation have generally not reported eGFR or CKD as a baseline variable or excluded such patients. Antiarrhythmic drug doses are adjusted based on pharmacokinetic data and clinical experience, with amiodarone being the only drug that does not require dose adjustment in patients with CKD or those receiving dialysis. Catheter ablation is feasible, although particular attention must be paid to fluid balance when using irrigated radiofrequency catheters. Anticoagulation in patients with CKD and AF is covered in **Section 6.8.4 (“Chronic Kidney Disease [CKD]/Kidney Failure”)**.

### 10.16. Anticoagulation Use in Patients With Liver Disease

Recommendations for Anticoagulation Use in Patients With Liver Disease		
Referenced studies that support the recommendations are summarized in the <a href="#">Online Data Supplement</a> .		
COR	LOE	Recommendations
2a	B-NR	1. For patients with AF who are at increased risk of systemic thromboembolism and mild or moderate liver disease (Child-Pugh* class A or B), OAC therapy is reasonable in the absence of clinically significant liver disease–induced coagulopathy or thrombocytopenia. <sup>1-7</sup>
2a	B-NR	2. For patients with AF who are at increased risk of systemic thromboembolism and mild or moderate liver disease (Child-Pugh class A or B) and who are deemed to be candidates for anticoagulation, it is reasonable to prescribe DOACs (Child-Pugh class A: any DOAC; Child-Pugh class B: apixaban, dabigatran, or edoxaban) over warfarin. <sup>1,7-11</sup>
3: Harm	C-LD	3. For patients with AF and moderate liver disease (Child-Pugh class B) at increased risk of systemic thromboembolism, rivaroxaban is contraindicated due to the potentially increased risk of bleeding. <sup>12</sup>

\*Child-Pugh scoring: the severity of liver disease, primarily cirrhosis in patients with diagnosed liver disease. Child-Pugh A (mild): 5-6 points; Child-Pugh B (moderate): 7-9 points; Child-Pugh C (severe): 10-15 points. The score is based on the 5 variables: encephalopathy (none=1 point, grade 1 and 2=2 points, grade 3 and 4=3 points); ascites (none=1 point, slight=2 points, moderate=3 points); total bilirubin (<2 mg/mL=1 point, 2-3 mg/mL=2 points, >3 mg/mL=3 points); albumin (>3.5 mg/mL=1 point, 2.8-3.5 mg/mL=2 points, <2.8 mg/mL=3 points); INR (<1.7=1 point, INR 1.7-2.2=2 points, INR >2.2=3 points).

## Synopsis

No RCT has evaluated the use of OACs in patients with AF and liver disease. Three observational studies and 1 meta-analysis of observational studies have compared OAC therapy with no OAC therapy in patients with AF and active liver disease or a history of liver disease.<sup>1-4</sup> In addition, 3 observational studies have compared OAC therapy in patients with liver disease to those without liver disease.<sup>5-7</sup> In general, anticoagulation has been associated with lower risks of ischemic stroke or thromboembolism but was also associated with a significantly higher risk of major bleeding or ICH compared with no oral anticoagulation therapy in patients with AF and liver disease. Oral factor Xa inhibitors undergo hepatic metabolism, and impaired liver function may increase their plasma concentrations and the risk of bleeding. Pivotal clinical trials for DOACs excluded patients with active liver disease. Four postmarketing retrospective studies and 2 meta-analyses have evaluated the comparison between DOACs and VKAs in this population, and they showed DOACs were associated with a lower risk of major bleeding or ICH.<sup>1,7-11</sup> Limited data exist on the safety of DOAC in severe liver disease. The uses of DOACs based on a Child-Pugh Score are summarized in Table 13 (Section 6.3.1.1. “**Considerations in Managing Anticoagulation**”).

## Recommendation-Specific Supportive Text

1. A meta-analysis showed that VKA use was significantly associated with lower risks of ischemic stroke or thromboembolism but was also associated with significantly higher risks of major bleeding or ICH in patients with AF and liver disease compared with no oral anticoagulation therapy.<sup>7</sup> A large-scale retrospective study also corroborated that OAC use was significantly associated with a lower risk of stroke or all-cause mortality in patients with AF and cirrhosis.<sup>3</sup> VKA use in the liver fibrosis group was associated with a higher risk of the composite cardiovascular events and major bleeding than in the nonliver fibrosis group.<sup>4</sup> However, no significant difference in the composite cardiovascular events and major bleeding between the 2 groups receiving DOACs was found. The efficacy and safety of VKAs or DOACs were not affected by nonalcohol fatty liver disease status.<sup>5</sup> The subgroup analysis of the meta-analysis found that the risk of major bleeding was not affected by the presence of esophageal varices.<sup>13</sup>
2. A meta-analysis found no significant difference in the risk of ischemic stroke and thromboembolism between DOACs and VKAs (OR, 0.82 [95% CI, 0.36-1.88];  $P=0.64$ ) in patients with almost exclusively mild-to-moderate liver disease (Child-Pugh class A-B), but DOAC use was associated with lower risks of major bleeding (OR, 0.54 [95% CI, 0.38-0.75];  $P=0.0003$ ) and ICH (OR, 0.35 [95% CI, 0.23-0.53];  $P<0.0001$ )

compared with the warfarin group.<sup>7</sup> Another meta-analysis showed that, in patients with exclusively mild-to-moderate cirrhosis (Child-Pugh score A-B), DOAC use was associated with lower risks of ischemic stroke (HR, 0.62 [95% CI, 0.10-0.90]), major bleeding (HR, 0.64 [95% CI, 0.57-0.72]), or ICH (HR, 0.49 [95% CI, 0.40-0.59]) compared with warfarin.<sup>11</sup> DOACs are reasonable oral anticoagulation agents in patients with AF and mild-to-moderate liver disease (Child-Pugh class A-B). However, data on DOACs are lacking on patients with AF and severe liver disease (Child-Pugh class C).

3. Rivaroxaban is currently avoided in patients with moderate liver disease (Child-Pugh class B). Rivaroxaban AUC significantly increased by 2.27-fold after a single dose of rivaroxaban 10 mg in patients with moderate liver disease compared with healthy subjects.<sup>12</sup> Although the FDA labeling recommends avoiding edoxaban in patients with moderate liver disease due to the concern of underlying coagulopathy, the edoxaban AUC was not significantly increased after a single dose of edoxaban 15 mg in patients with moderate liver disease compared with healthy subjects.<sup>14</sup> Apixaban AUC was not significantly increased after a single dose of apixaban 5 mg in subjects with mild and moderate liver disease (Child-Pugh class A and B) compared with healthy subjects.<sup>15</sup> Dabigatran AUC was also not significantly different after a single dose of dabigatran 150 mg in patients with moderate liver disease (Child-Pugh class B) compared with that in healthy subjects.<sup>16</sup>

## 11. FUTURE RESEARCH NEEDS

Enormous progress and important advances have been made in recent years on the understanding of mechanisms and on the prevention and management of AF, including substantial progress since the 2014 guideline, as well as the 2019 focused update. Although the writing committee has tried to make significant progress in this current guideline to address many of the gaps in the clinical management of AF, important gaps in knowledge remain and are listed below.

1. **AF as a disease continuum:** AF must be seen as a disease continuum, yet historically the emphasis has been on rhythm management. More evidence is needed on how to best improve in other aspects of AF care, such as prevention, modification of risk factors, and how to incorporate holistic approaches to AF management into daily clinical practice.
2. **Downstream consequences:** The downstream consequences of AF over the long term must be better studied and defined. Most studies generally focus on short-term effects of therapy, usually 6 to 12 months. Many long-term consequences of AF

- remain poorly characterized, such as dementia and valvular insufficiency.
3. **Better goal and outcome definition:** Historically, ablation failure has been defined as having 30 seconds of AF identified during a follow-up period. However, that number might be too simplistic because AF burden may be a more important metric and because the 30-second metric might not reflect significant burden reduction that may be observed in many patients. Patient-oriented outcomes would also be more important, such as QOL.
  4. **Role of risk modifiers in AF stroke prevention:** Great variation exists in risk of stroke depending on nonbinary or dynamic risk factors. Yet it is unclear how to best manage patients accordingly. For example, how should risk of stroke be assessed in a person with hypertension in whom the BP is very well controlled? Or, perhaps, how do we incorporate AF burden on the risk calculation?
  5. **Individualization of AF and stroke risk:** Although some studies have demonstrated an effective role of biomarkers in predicting AF and stroke, how to incorporate these findings into clinical practice remains elusive. Similarly, how to incorporate other clinical markers of atrial cardiopathy into clinical practice must be better defined, as well as clarification as to how these nontraditional risk factors help better stratify patient risk.
  6. **Incorporating other stroke risk scores:** The ubiquitous nature and simplicity of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score have diminished with consideration of other scores of potential utility, better c-statistics, and with potential advantages in particular populations. Additional studies are needed to better take advantage of scores for specific groups, scores that could potentially be incorporated into the electronic medical record, and perhaps some with the potential benefit of better discriminating the true low-risk patients.
  7. **Surgical exclusion and LAAO:** Increasingly available evidence has demonstrated the benefit of surgical LAA exclusion for stroke prevention, but the most scientifically rigorous trials included patients who received concomitant anticoagulation. More evidence is needed on the magnitude of benefit of LAA exclusion in preventing stroke in patients who have contraindications to anticoagulation and how to best manage those patients around rhythm-control interventions, such as cardioversion. Clinicians would also like to see additional data on pLAO, particularly peri-implant stroke management and longer-term outcomes in patients in whom periprocedure anticoagulation is not possible.
  8. **Subclinical AF:** What magnitude of AF burden mandates stroke prevention therapy in patients with subclinical AF must be better defined. Certainly, large general risk categories have been identified, and general guidelines exist, but extensive practice variations remain, and more precise recommendations for the community are needed. In addition, the role and impact on outcomes of AF screening in general and poststroke should be better defined.
  9. **Use and applicability of consumer-based wearable heart monitoring devices:** These devices are now widespread and are used to diagnose and monitor response to therapy in patients with AF. Validation on the accuracy of the most common available technologies is needed. How to best use these devices in practice, including for AF screening, must be better defined.
  10. **Standardization of ablation procedures:** Great practice variation exists on how AF ablation procedures are performed, either as first or repeat procedures. Large registries and more data are required to better define standards of care in this field. Many interventions, such as extra ablation lines, are still performed despite limited data demonstrating efficacy, whereas the best approaches to persistent AF and repeat ablation are poorly defined.
  11. **Candidates for ablation:** We must better identify clinical markers to better identify when catheter ablation is unlikely to benefit patients and define specific criteria for candidacy for first time and repeat procedures.
  12. **Artificial intelligence for AF management:** Artificial intelligence could potentially be used to better tailor therapy to the individual patient, taking into consideration numerous factors that may better select candidates for therapeutic approaches, such as anticoagulation versus LAO, rhythm versus rate control, catheter ablation versus medical therapy, modification of risk factors, genetics, and others.
  13. **Strategies for anticoagulation:** Ongoing clinical trials are assessing different strategies for oral anticoagulation in persons who have undergone catheter ablation, including the OCEAN (Optimal AntiCoagulation for Enhanced-Risk Patients Post-Catheter Ablation for Atrial Fibrillation) trial (NCT02168829)<sup>1</sup> and ODIn-AF (Prevention of Silent Cerebral Thromboembolism by Oral Anticoagulation With Dabigatran After Pulmonary Vein Isolation for Atrial Fibrillation) (NCT02067182)<sup>2</sup> trial, because it is unclear in whom anticoagulation can be discontinued after successful ablation. Several studies also have investigated the use of intermittent or continuous rhythm monitoring to guide oral anticoagulation in persons with AF, including those who have undergone ablation.<sup>3,4</sup> These so-called “PITP” or “electrocardiographic-guided” approaches are investigational. Ongoing clinical trials like REACT-AF (Rhythm Evaluation for Anticoagulation

Therapy for Atrial Fibrillation) will help determine whether they are suitable for clinical practice. Also, anticoagulation/DOAC use in pregnancy needs to be investigated because it is currently contraindicated in view of lack of data on safety.

14. **Sleep:** Among patients with AF and SDB, the impact of treatment of SDB on maintenance of sinus rhythm and on general cardiovascular outcomes remains uncertain. Most studies have been observational, which introduces confounding factors. Once diagnosed, the adherence to treatment for SDB is also suboptimal.
15. **SDM and decision aids:** Decision aids are perceived as important tools to better inform patients about options for AF management; yet, it is unclear if those tools improve clinical outcomes. Most decision aids developed for AF focus on anticoagulation; there is a paucity of validated decision aids, including for AF rhythm management using antiarrhythmic drugs or ablation.
16. **Genetic testing:** The use and applicability of consumer-based or targeted genetic testing for AF remains uncertain. Polygenic risk scores can indicate higher risk for AF, but the use of genetic testing to impact clinical surveillance, management, and clinical outcomes remains uncertain.
17. **Race, ethnicity, gender, and sex differences:** In sexual- and gender-diverse individuals, additional research is recommended to identify the incidence and outcomes of AF as well as the impact of gender-affirming therapies on arrhythmia incidence and outcomes. Additional data across racial and ethnic groups should also be encouraged.
18. **Standardized measures:** For patients with AF, a standardized measure might be useful to assess symptoms and/or QOL and impact of management strategies.
19. **SDOH:** The measurement and impact of SDOH in AF is underutilized and understudied.

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**Appendix 1. Author Relationships With Industry and Other Entities—2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation**

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
José A. Joglar, Chair	UT Southwestern Medical Center— Professor and Vice Chair for Clinical Affairs at Parkland, Department of Internal Medicine Elizabeth Thaxton and Ellis Batten Page Professorship in Cardiac Electrophysiology Research Director of Cardiac Electrophysiology Fellowship Program	None	None	None	None	None	None
Mina K. Chung, Vice Chair	Cleveland Clinic, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University—Cardiac Pacing and Electrophysiology Department of Cardiovascular Medicine, Heart and Vascular Institute Department of Cardiovascular & Metabolic Sciences, Lerner Research Institute	NOT RELEVANT • ABIM* • Geisinger Health Systems	None	None	NOT RELEVANT • AHA* • NIH*	NOT RELEVANT • Abbott‡ • AHA* • Biosense Webster‡ • Boston Scientific‡ • Elsevier • FNRA • Hamilton Health Sciences/PHRI‡ • HRS† • Medtronic‡ • Myocardial Solutions‡ • UptoDate	None
Anastasia L. Armbruster	St. Louis College of Pharmacy AT UHSP—Associate Professor, Pharmacy Practice	None	RELEVANT • AstraZeneca	None	None	None	None
Emelia J. Benjamin	Boston University Schools of Medicine and Public Health, The Framingham Heart Study—Associate Provost for Faculty Development, Boston University Medical Campus Vice Chair, Faculty Development and Diversity, Department of Medicine Cardiologist, Boston Medical Center, Boston University Medical Group	None	None	None	NOT RELEVANT • AHA* • Cardia (DSMB)† • NIH*	NOT RELEVANT • <i>Circulation</i> † • <i>European Heart Journal</i> † • <i>Nature Reviews Cardiology</i> †	None
Janice Y. Chyou	Icahn School of Medicine at Mount Sinai—Assistant Clinical Professor, Cardiac Electrophysiology, Cardiology Heart and Heart Rhythm Care	None	None	None	None	NOT RELEVANT • AHA† • HRS† • McGraw Hill	None
Edmond M. Cronin	Temple University Hospital—Main Campus—Temple Heart & Vascular Institute	RELEVANT • Medtronic	None	None	None	NOT RELEVANT • Biosense Webster§ • Janssen Pharmaceuticals§ • Medtronic§	None
Anita Deswal	The University of Texas MD Anderson Cancer Center—Chair, Department of Cardiology Ting Tsung and Wei Fong Chao Distinguished Chair Professor of Medicine	None	None	None	None	NOT RELEVANT • ACC* • CPRIT* • NIH	None

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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
Lee Eckhardt	University of Wisconsin-Madison—Associate Professor of Medicine Gary and Marie Weiner Professor in Cardiovascular Medicine Research Cellular and Molecular Arrhythmia Research Program Division of Cardiovascular Medicine	None	None	None	None	None	None
Zachary D. Goldberger	University of Wisconsin-Madison School of Medicine and Public Health Division of Cardiovascular Medicine/Electrophysiology—Associate Professor of Medicine Program Director, Cardiovascular Disease Fellowship Associate Program Director, Clinical Cardiac Electrophysiology Fellowship	None	None	None	None	None	None
Rakesh Gopinathannair	University of Louisville—Associate Professor of Medicine (Adjunct) University of Missouri-Columbia—Cardiac EP Lab Director, Kansas City Heart Rhythm Institute EP Medical Director, Research Medical Center Professor of Medicine	<p>RELEVANT</p> <ul style="list-style-type: none"> <li>Abbott*</li> <li>Biosense Webster</li> <li>Biotronik</li> <li>Boston Scientific*</li> <li>Johnson &amp; Johnson</li> <li>Pfizer*</li> <li>Sanofi-Aventis</li> <li>Zollt</li> </ul> <p>NOT RELEVANT</p> <ul style="list-style-type: none"> <li>Academy for Continued Healthcare Learning</li> </ul>	<p>RELEVANT</p> <ul style="list-style-type: none"> <li>Pfizer</li> <li>Zollt</li> </ul>	None	None	<p>NOT RELEVANT</p> <ul style="list-style-type: none"> <li>AHA</li> <li>Atricure</li> <li>Geisinger Health System</li> <li>HRS</li> <li>Janssen Pharmaceuticals</li> <li>Kowa Pharmaceuticals</li> <li>Medtronic</li> <li>Methodist Health System</li> <li>Novartis</li> <li>Pacematet</li> <li>Philips</li> </ul>	None
Bulent Gorenek	Eskisehir Osmangazi University School of Medicine—Cardiovascular Diseases, Arrhythmias in Intensive Cardiac Care Unit. Professor in Cardiology Vice Director, Cardiology Department	<p>RELEVANT</p> <ul style="list-style-type: none"> <li>AstraZeneca</li> <li>Bayer</li> <li>Daichi Sankyo</li> <li>Roche</li> </ul> <p>NOT RELEVANT</p> <ul style="list-style-type: none"> <li>Sandoz</li> </ul>	None	None	None	None	None
Paul L. Hess	University of Colorado School of Medicine Seattle-Denver Center of Innovation Rocky Mountain Regional VA Medical Center—Associate Professor of Medicine	None	None	None	None	<p>NOT RELEVANT</p> <ul style="list-style-type: none"> <li>CPC Clinical Research*</li> <li>VA CSP</li> </ul>	None
Mark Hlatky	Stanford University School of Medicine—Professor of Health Policy, and of Medicine (Cardiovascular Medicine), and, by courtesy, of Epidemiology and Population Health	<p>RELEVANT</p> <ul style="list-style-type: none"> <li>Boehringer Ingelheim</li> </ul> <p>NOT RELEVANT</p> <ul style="list-style-type: none"> <li>BCBS Center for Effectiveness Evaluation*</li> </ul>	None	None	None	<p>NOT RELEVANT</p> <ul style="list-style-type: none"> <li>George Institute</li> </ul>	None

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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
Gail Hogan	Patient Representative	None	None	None	None	NOT RELEVANT • Ohio State University Wexner Medical Center	None
Chinwe Ibeh	Columbia University CUIMC/ Neurological Institute of New York—Assistant Professor of Neurology Department of Neurology Division of Stroke and Cerebrovascular Disease	None	None	None	None	None	None
Julia H. Indik	University of Arizona College of Medicine—Professor of Medicine Director, Cardiovascular Disease Fellowship Program Division of Cardiology/Sarver Heart Center	None	None	None	None	None	None
Kazuhiko Kido	West Virginia University—Cardiology Pharmacy Specialist, Advanced Heart Failure and Pulmonary Hypertension Clinical Assistant Professor of Clinical Pharmacy	None	None	None	None	None	None
Fred Kusumoto	Mayo Clinic Jacksonville	None	None	None	NOT RELEVANT • EP Research Foundation (TAP-CHF Trial)	NOT RELEVANT • Biotronik\$	None
Mark S. Link	UT Southwestern Medical Center, Dallas—Professor of Medicine. Director, Cardiac Electrophysiology. Laurence and Susan Hirsch/Centex Distinguished Chair in Heart Disease Department of Internal Medicine, Division of Cardiology	None	None	None	None	NOT RELEVANT • <i>Circulation</i> * • <i>Journal Watch Cardiology</i> • <i>UpToDate</i> *	None
Kathleen T. Linta	Patient Representative	None	None	None	None	None	None
Gregory M. Marcus	University of California, San Francisco—Professor of Medicine in Residence Associate Chief of Cardiology for Research Endowed Professor of Atrial Fibrillation Research	NOT RELEVANT • InCarda*  RELEVANT • Johnson & Johnson	None	None	NOT RELEVANT • Baylis*	NOT RELEVANT • InCarda*	None
Patrick M. McCarthy	Northwestern Medicine—Executive Director, Bluhm Cardiovascular Institute Vice President, Northwestern Medical Group Chief, Division of Cardiac Surgery Heller-Sacks Professor of Surgery	RELEVANT • Abbott • Attricure • Edwards Lifesciences* • Medtronic	None	None	RELEVANT • Abbott†	NOT RELEVANT • Egnite • Siemens  RELEVANT • Edwards Lifesciences*	None
Nimesh Patel	UT Southwestern Medical Center—Assistant Professor of Medicine, Clinical Cardiac Electrophysiology	None	None	None	None	NOT RELEVANT • Abbvie\$ • Novo Nordisk\$	None

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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
Kristen K. Patton	University of Washington—Professor of Medicine	None	None	None	None	NOT RELEVANT • ACGME† • AHA† • HRS† • JAMA • US FDA CDRH*	None
Marco V. Perez	Stanford University—Associate Professor—University Med Line Department of Medicine, Med/Cardiovascular	RELEVANT • Biotronik* • Boehringer Ingelheim* • Boston Scientific* • Bristol Myers Squibb • Johnson & Johnson	None	NOT RELEVANT • Feather Health*	NOT RELEVANT • Apple* • NIH*	None	NOT RELEVANT Defendant, Digital health tools case, 2021
Jonathan P. Piccini	Duke University School of Medicine— Department of Medicine	RELEVANT • Abbott* • Abbvie • ARCA Biopharma • Biotronik • Bristol Myers Squibb* • Electrophysiology Frontiers* • Itamar Medical • Medtronic* • Milestone Medical • Philips* • Recor • Sanofi-Aventis*  NOT RELEVANT • UpToDate*	None	None	RELEVANT • Abbott* • Bayer* • Boston Scientific* • iRhythm* • Philips*  NOT RELEVANT • AAMI* • Acutus Medical, Inc.§ • AHA* • Atricure§ • Element Science (DSMB)* • LivaNova (CEAC)* • LSI Solutions§	NOT RELEVANT • LivaNova (CEAC)*	None
Andrea M. Russo	Cooper University—Professor of Medicine Director, Electrophysiology and Arrhythmia Services Director of Research, Cooper Heart Institute Program Director, Clinical Cardiac Electrophysiology Fellowship	RELEVANT • Abbott • Atricure • Biosense Webster • Biotronik • Boston Scientific • Bristol Myers Squibb • Medtronic • Pfizer • Sanofi  NOT RELEVANT • Medical Device Business Services, Inc. • Pacemate	None	None	None	NOT RELEVANT • ABIM • Boston Scientific† • Kestra† • MedLynx† • UpToDate	None
Prashanthan Sanders	The University of Adelaide Royal Adelaide Hospital— Director, Centre for Heart Rhythm Disorders Director, Cardiac Electrophysiology & Pacing NHMRC Practitioner Fellow	None	None	None	RELEVANT • Abbott* • BD* • Boston Scientific* • Medtronic*	RELEVANT • Abbott • Boston Scientific • CathRX • Medtronic  NOT RELEVANT • Pacemate	None
Megan M. Streur	University of Washington—Assistant Professor and Endowed Faculty Fellow for Cardiovascular Disease Prevention Department of Biobehavioral Nursing and Health Informatics Adjunct Assistant Professor, Cardiac Electrophysiology Department of Medicine	None	None	None	NOT RELEVANT • NIH/NINR*	None	None

(Continued)

**Appendix 1. Continued**

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Kevin L. Thomas	Duke University School of Medicine— Professor of Medicine Vice Dean for Diversity, Equity and Inclusion Member in the Duke Clinical Research Institute	RELEVANT • Biosense Webster • Johnson & Johnson	None	None	None	NOT RELEVANT • Community Health Coalition†	None
Sabrina Times§	American Heart Association/ American College of Cardiology Science and Health Advisor, Guidelines	None	None	None	None	None	None
James E. Tisdale	Purdue University College of Pharmacy—Professor Indiana University School of Medicine—Adjunct Professor	None	None	None	NOT RELEVANT • AHRQ* • AHA* • NIH*	NOT RELEVANT • American Society for Health-Systems Pharmacists • AZCert • Crediblemeds.org† • Nova Southeastern University • <i>Pharmacotherapy Journal</i> • Pharmacotherapy Publications, Inc. †	None
Anne Marie Valente	Boston Children's Hospital, Brigham and Women's Hospital—Co-Director, Pregnancy and Cardiovascular Disease Program Brigham and Women's Hospital Associate Professor, Medicine and Pediatrics Harvard Medical School Section Chief, Boston Adult Congenital Heart Disease (BACH) and Pulmonary Hypertension Program	NOT RELEVANT • Elsevier*	None	None	None	NOT RELEVANT • Elsevier* • <i>Journal of the ACC*</i> • United Therapeutics§	None
David R. Van Wagoner	Cleveland Clinic, ND-50— Department of Cardiovascular & Metabolic Sciences	None	None	None	NOT RELEVANT • AHA* • NIH/NHLBI*	None	None

This table represents all relationships of committee members with industry and other entities that were reported by authors, including those not deemed to be relevant to this document, at the time this document was under development. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥\$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. Please refer to <https://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.

\*Significant relationship.

†No financial benefit.

‡This disclosure was entered under the Clinical Trial Enroller category in the ACC's disclosure system. To appear in this category, the author acknowledges that there is no direct or institutional relationship with the trial sponsor as defined in the (ACCF or AHA/ACC) Disclosure Policy for Writing Committees.

§Sabrina Times is an AHA/ACC joint staff member and acts as the Science and Health Advisor for the "2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation." No relevant relationships to report. Nonvoting author on measures and not included/counted in the RWI balance for this writing committee.

AAMI indicates Association for the Advancement of Medical Instrumentation; ABIM, American Board of Internal Medicine; ACC, American College of Cardiology; ACGME, Accreditation Council for Graduate Medical Education; AHA, American Heart Association; AHRQ, Agency for Health Research and Quality; BCBS, Blue Cross Blue Shield; BD, Becton Dickinson; CDRH, Center for Devices and Radiological Health; CEAC, Clinical Event Adjudication Committee; CPRIT, Cancer Prevention and Research Institute of Texas; CUIMC, Columbia University Irving Medical Center; DSMB, data and safety monitoring board; EP, electrophysiology; FDA, US Food and Drug Administration; FNRA, French National Research Agency; HRS, Heart Rhythm Society; *JAMA*, *Journal of the American Medical Association*; NIH, National Institutes of Health; NINR, National Institute of Nursing Research; NHLBI, National Heart, Lung, and Blood Institute; NHMRC, National Health and Medical Research Council; PHRI, Population Health Research Institute; UHSP, University of Health Science and Pharmacy in St. Louis; UT, University of Texas; and VA CSP, Veterans Affairs Cooperative Studies Program.

**Appendix 2. Reviewer Relationships With Industry and Other Entities (Comprehensive)–2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation**

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Andrew D. Krahn	AHA/ACC Atrial Fibrillation Peer Review Committee Chair	University of British Columbia	None	None	• CCS* • HRS*	None	None	None
Jason G. Andrade	AHA/ACC Atrial Fibrillation Peer Review Committee	University of Montreal	• Biosense Webster • Medtronic	• Bayer • Bristol Myers Squibb/Pfizer Alliance • Servier	None	• Medtronic†	None	None
Craig J. Beavers	AHA/ACC Atrial Fibrillation Peer Review Committee, representing ACCP	University of Kentucky College of Pharmacy	None	None	None	None	None	None
James M. Bischoff	AHA/ACC Atrial Fibrillation Peer Review Committee, Patient Representative	Superintendent, Retired	None	None	None	None	None	None
T. Jared Bunch	AHA/ACC Atrial Fibrillation Peer Review Committee, representing HRS	University of Utah School of Medicine	None	None	None	• Altathera† • Boehringer Ingelheim†	• Abbott‡ • Altathera‡ • Cardiva‡ • St. Jude's Medical‡	None
Kristen Bova Campbell	AHA/ACC Atrial Fibrillation Peer Review Committee	Duke University	• Wolters Kluwer	None	None	None	None	None
Lin Yee Chen	AHA/ACC Atrial Fibrillation Peer Review Committee	University of Minnesota School of Medicine	None	None	None	None	• NIH†	None
Robin Dharia	AHA/ACC Atrial Fibrillation Peer Review Committee	Thomas Jefferson University	None	None	None	None	• NIH‡	None
Michael P. Dorsch	AHA/ACC Atrial Fibrillation Peer Review Committee, representing JCPM	University of Michigan	None	None	None	None	None	None
Edward P. Gerstenfeld	AHA/ACC Atrial Fibrillation Peer Review Committee	University of California San Francisco	• Biosense Webster† • Medtronic • St. Jude Medical	None	None	• Abbott (DSMB)† • Adagio* • Boston Scientific* • ThermoMedical (DSMB)†	• Boston Scientific*	None
Aubrey E. Jones	AHA/ACC Atrial Fibrillation Peer Review Committee	University of Utah College of Pharmacy	None	None	None	• AHRQ† • NIH-NHLBI†	None	None
Stephanie Dwyer Kaluzna	AHA/ACC Atrial Fibrillation Peer Review Committee	University of Illinois Chicago College of Pharmacy	None	None	None	None	None	None
Luke Masha	AHA/ACC Atrial Fibrillation Peer Review Committee	Oregon Health & Science University	None	None	None	None	• Ancora‡ • Endotronix‡	None
Isabelle Nault	AHA/ACC Atrial Fibrillation Peer Review Committee	Quebec Heart and Lung Institute	• Bristol Myers Squibb • Pfizer	• Bayer† • Biosense Webster • Medtronic • Servier†	None	None	None	None

(Continued)

## Appendix 2. Continued

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Peter A. Noseworthy	AHA/ACC Atrial Fibrillation Peer Review Committee	Mayo Clinic	None	None	None	None	<ul style="list-style-type: none"> <li>• Anumana*</li> <li>• Milestone‡</li> </ul>	None
Cara N. Pellegrini	AHA/ACC Atrial Fibrillation Peer Review Committee	University of California San Francisco	<ul style="list-style-type: none"> <li>• Abbott</li> <li>• Biosense Webster</li> <li>• Cook Medical</li> <li>• Medtronic</li> </ul>	None	None	None	None	None
Stylianos E. Tzeis	AHA/ACC Atrial Fibrillation Peer Review Committee	Mitera Hospital	<ul style="list-style-type: none"> <li>• Pfizer</li> </ul>	None	None	None	<ul style="list-style-type: none"> <li>• Bayer‡</li> </ul>	None
Annabelle Santos Volgman	AHA/ACC Atrial Fibrillation Peer Review Committee	Rush University Medical Center	<ul style="list-style-type: none"> <li>• Bristol Myers Squibb Foundation DCICDP</li> <li>• Janssen Pharmaceuticals</li> <li>• Merck</li> <li>• Pfizer</li> <li>• Sanofi</li> <li>• Aventist</li> </ul>	None	None	<ul style="list-style-type: none"> <li>• NIH†</li> </ul>	<ul style="list-style-type: none"> <li>• Apple*</li> <li>• Novartis‡</li> </ul>	None
Emily P. Zeitler	AHA/ACC Atrial Fibrillation Peer Review Committee	Dartmouth Hitchcock Medical Center	<ul style="list-style-type: none"> <li>• Abbott</li> <li>• Biosense Webster</li> <li>• Medtronic</li> </ul>	None	None	<ul style="list-style-type: none"> <li>• Boston Scientific</li> <li>• Sanofi</li> <li>• Aventus*</li> </ul>	None	None

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\*No financial benefit.

†Significant relationship.

‡This disclosure was entered under the Clinical Trial Enroller category in the ACC's disclosure system. To appear in this category, the author acknowledges that there is no direct or institutional relationship with the trial sponsor as defined in the (ACCF or AHA/ACC) Disclosure Policy for Writing Committees.

ACC indicates American College of Cardiology; ACCF, American College of Cardiology Foundation; AACP, American Association of Colleges of Pharmacy; AHA, American Heart Association; AHRQ, Agency for Healthcare Research and Quality; CCS, Canadian Cardiovascular Society; DCICDP, Diverse Clinical Investigator Career Development Program; DSMB, data and safety monitoring board; HRS, Heart Rhythm Society; JCPM, ACC/AHA Joint Committee on Performance Measures, NHLBI, National Heart, Lung, and Blood Institute; and NIH, National Institutes of Health.