Accepted Manuscript

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

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

PII: S0735-1097(14)01740-9

DOI: 10.1016/j.jacc.2014.03.022

Reference: JAC 20031

To appear in: *Journal of the American College of Cardiology*

Please cite this article as: January CT, Wann LS, Alpert JS, Calkins H, Cleveland Jr JC, Cigarroa JE, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW, 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation, *Journal of the American College of Cardiology* (2014), doi: 10.1016/j.jacc.2014.03.022.

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

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

Developed in Collaboration With the Society of Thoracic Surgeons

WRITING COMMITTEE MEMBERS*

Craig T. January, MD, PhD, FACC, *Chair*
L. Samuel Wann, MD, MACC, FAHA, *Vice Chair**

Joseph S. Alpert, MD, FACC, FAHA*†
Hugh Calkins, MD, FACC, FAHA, FHRS*‡§
Joseph C. Cleveland, Jr, MD, FACC‖
Joaquin E. Cigarroa, MD, FACC†
Jamie B. Conti, MD, FACC, FHRS*†
Patrick T. Ellinor, MD, PhD, FAHA‡
Michael D. Ezekowitz, MB, ChB, FACC, FAHA*†
Michael E. Field, MD, FACC, FHRS†
Katherine T. Murray, MD, FACC, FAHA, FHRS†
Ralph L. Sacco, MD, FAHA†
William G. Stevenson, MD, FACC, FAHA, FHRS*¶
Patrick J. Tchou, MD, FACC‡
Cynthia M. Tracy, MD, FACC, FAHA†
Clyde W. Yancy, MD, FACC, FAHA†

ACC/AHA TASK FORCE MEMBERS

Jeffrey L. Anderson, MD, FACC, FAHA, *Chair*
Jonathan L. Halperin, MD, FACC, FAHA, *Chair-Elect*

Nancy M. Albert, PhD, CCNS, CCRN, FAHA
Biykem Bozkurt, MD, PhD, FACC, FAHA
Ralph G. Brindis, MD, MPH, MACC
Mark A. Creager, MD, FACC, FAHA**
Lesley H. Curtis, PhD
David DeMets, PhD
Robert A. Guyton, MD, FACC**
Judith S. Hochman, MD, FACC, FAHA
Richard J. Kovacs, MD, FACC, FAHA
E. Magnus Ohman, MD, FACC
Susan J. Pressler, PhD, RN, FAHA
Frank W. Sellke, MD, FACC, FAHA
Win-Kuang Shen, MD, FACC, FAHA
William G. Stevenson, MD, FACC, FAHA**
Clyde W. Yancy, MD, FACC, FAHA**

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply; see Appendix 1 for recusal information. †ACC/AHA Representative. ‡Heart Rhythm Society Representative. §ACC/AHA Task Force on Performance Measures Liaison. ‖Society of Thoracic Surgeons Representative. ¶ACC/AHA Task Force on Practice Guidelines Liaison. **Former Task Force member during the writing effort.

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

The American College of Cardiology requests that this document be cited as follows: January CT, Wann LS, Alpert JS, Calkins H, Cleveland JC, Cigarroa JE, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014; ●●:●●●●–●●●●.

This article is copublished in *Circulation.*

Copies: This document is available on the World Wide Web sites of the American College of Cardiology (www.cardiosource.org), the American Heart Association (my.americanheart.org), and the Heart Rhythm Society (www.hrsonline.org). A copy of the document is available at http://my.americanheart.org/statements by selecting either the “By Topic” link or the “By Publication Date” link. For copies of this document, please contact the Elsevier Inc. Reprint Department, fax (212) 633-3820, e-mail reprints@elsevier.com.

January, CT et al.
2014 AHA/ACC/HRS Atrial Fibrillation Guideline

January, CT et al.
2014 AHA/ACC/HRS Atrial Fibrillation Guideline

Table of Contents

Preamble

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

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

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

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

LOE C recommendations and no references are cited. The schema for COR and LOE is summarized in Table 1, which also provides suggested phrases for writing recommendations within each COR.

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

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

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

The ACC/AHA practice guidelines are intended to assist clinicians in clinical decision making by describing a range of generally acceptable approaches to the diagnosis, management, and prevention of specific diseases or conditions. The guidelines attempt to define practices that meet the needs of most patients in most circumstances. The ultimate judgment about care of a particular patient must be made by the clinician and patient in light of all the circumstances presented by that patient. As a result, situations may arise in which deviations from these guidelines may be appropriate. Clinical decision making should involve consideration of the quality and availability of expertise in the area where care is provided. When these guidelines are used as the basis for regulatory or payer decisions, the goal should be improvement in quality of care. The Task Force recognizes that situations arise in which additional data are needed to inform patient care more effectively; these areas are identified within each respective guideline when appropriate.

Prescribed courses of treatment in accordance with these recommendations are effective only if followed. Because lack of patient understanding and adherence may adversely affect outcomes, clinicians should make every effort to engage the patient's active participation in prescribed medical regimens and lifestyles. In addition, patients should be informed of the risks, benefits, and alternatives to a particular treatment and should be involved in shared decision making whenever feasible, particularly for COR IIa and IIb, for which the benefit-to-risk ratio may be lower.

The Task Force makes every effort to avoid actual, potential, or perceived conflicts of interest that may arise as a result of relationships with industry and other entities (RWI) among the members of the writing

committee. All writing committee members and peer reviewers of the guideline are required to disclose all current healthcare-related relationships, including those existing 12 months before initiation of the writing effort.

In December 2009, the ACC and AHA implemented a new RWI policy that requires the writing committee chair plus a minimum of 50% of the writing committee to have no relevant RWI (Appendix 1 includes the ACC/AHA definition of *relevance*). The Task Force and all writing committee members review their respective RWI disclosures during each conference call and/or meeting of the writing committee, and members provide updates to their RWI as changes occur. All guideline recommendations require a confidential vote by the writing committee and require approval by a consensus of the voting members. Members may not draft or vote on any recommendations pertaining to their RWI. Members who recused themselves from voting are indicated in the list of writing committee members, and specific section recusals are noted in Appendix 1. Authors' and peer reviewers' RWI pertinent to this guideline are disclosed in Appendixes 1 and 2. In addition, to ensure complete transparency, writing committee members' comprehensive disclosure information—including RWI not pertinent to this document—is available as an online supplement (http://jaccjacc.cardiosource.com/DataSupp/2014_AF_GL_RWI_Table_Comprehensive_Only_0319.pdf). Comprehensive disclosure information for the Task Force is also available online at http://www.cardiosource.org/en/ACC/About-ACC/Who-We-Are/Leadership/Guidelines-and-Documents-Task-Forces.aspx. The ACC and AHA exclusively sponsor the work of the writing committee, without commercial support. Writing committee members volunteered their time for this activity. Guidelines are official policy of both the ACC and AHA.

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

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

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

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

Table 1. Applying Classification of Recommendations and Level of Evidence

SIZE OF TREATMENT EFFECT

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

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes mellitus, history of prior myocardial infarction, history of heart failure, and prior aspirin use.
†For comparative-effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

Valvular Heart Disease	AHA/ACC	2014 (22)
Assessment of Cardiovascular Risk	ACC/AHA	2013 (23)
Lifestyle Management to Reduce Cardiovascular Risk	AHA/ACC	2013 (24)
Management of Overweight and Obesity in Adults	AHA/ACC/TOS	2013 (25)
Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults	ACC/AHA	2013 (26)
Statements		
Treatment of Atrial Fibrillation	AHRQ	2012 (7)
Oral Antithrombotic Agents for the Prevention of Stroke in Nonvalvular Atrial Fibrillation: a Science Advisory for Healthcare Professionals	AHA/ASA	2012 (27)
Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-Up, Definitions, Endpoints, and Research Trial Design	HRS/EHRA/ECAS	2012 (28)

*Includes the following sections: Catheter Ablation for AF/Atrial Flutter, Prevention and Treatment of AF Following Cardiac Surgery; Rate and Rhythm Management, Prevention of Stroke and Systemic Thromboembolism in AF and Flutter; Management of Recent-Onset AF and Flutter in the Emergency Department; Surgical Therapy; The Use of Antiplatelet Therapy in the Outpatient Setting; and Focused 2012 Update of the CCS AF Guidelines: Recommendations for Stroke Prevention and Rate/Rhythm Control.

AATS indicates American Association for Thoracic Surgery; ACC, American College of Cardiology; ACCF, American College of Cardiology Foundation; ACP, American College of Physicians; ACCP, American College of Chest Physicians; AHA, American Heart Association; AHRQ, Agency for Healthcare Research and Quality; ASA, American Stroke Association; AF, atrial fibrillation; CCS, Canadian Cardiology Society; ECAS, European Cardiac Arrhythmia Society; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; JNC, Joint National Committee; NHLBI, National Heart, Lung, and Blood Institute; PCNA, Preventive Cardiovascular Nurses Association; SCAI, Society for Cardiac Angiography and Interventions; STS, Society of Thoracic Surgeons, and TOS, The Obesity Society.

2. Background and Pathophysiology

AF is a common cardiac rhythm disturbance and increases in prevalence with advancing age. Approximately 1% of patients with AF are <60 years of age, whereas up to 12% of patients are 75 to 84 years of age (29). More than one third of patients with AF are ≥80 years of age (30, 31). In the United States, the percentage of Medicare Fee-for-Service beneficiaries with AF in 2010 was reported as 2% for those <65 years of age and 9 % for those ≥65 years of age (32). For individuals of European descent, the lifetime risk of developing AF after 40 years of age is 26% for men and 23% for women (33). In African Americans, although risk factors for AF are more prevalent, the AF incidence appears to be lower (34). AF is often associated with structural heart disease and other co-occurring chronic conditions (Table 3; see also http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/Downloads/2012Chartbook.pdf). The mechanisms causing and sustaining AF are multifactorial, and AF can be complex and difficult for clinicians to manage. AF symptoms range from non-existent to severe. Frequent hospitalizations, hemodynamic abnormalities, and thromboembolic events related to AF result in significant morbidity and mortality. AF is associated with a 5-fold increased risk of stroke (35) and stroke risk increases with age (36). AF-related stroke is likely to be more

severe than non–AF-related stroke (37). AF is also associated with a 3-fold risk of HF (38-40), and 2-fold increased risk of both dementia (41) and mortality (35). Hospitalizations with AF as the primary diagnosis are >467,000 annually in the United States, and AF is estimated to contribute to >99,000 deaths per year. Patients with AF are hospitalized twice as often as patients without AF; are 3 times more likely to have multiple admissions; and 2.1% of patients with AF died in the hospital compared to 0.1% without it (42, 43). AF is also expensive, adding approximately $8,700 per year (estimate from 2004 to 2006) for a patient with AF compared to a patient without AF. It is estimated that treating patients with AF adds $26 billion to the U.S. healthcare bill annually. AF affects between 2.7 million and 6.1 million American adults, and that number is expected to double over the next 25 years, adding further to the cost burden (42, 43).

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

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

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

AF indicates atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disorder; and HF, heart failure.
Reproduced with permission from the Centers for Medicare and Medicaid Services (44).

2.1. Definitions and Pathophysiology of AF

AF is a supraventricular tachyarrhythmia with uncoordinated atrial activation and consequently ineffective atrial contraction (4, 28, 30). Electrocardiogram (ECG) characteristics include: 1) irregular R-R intervals (when atrioventricular [AV] conduction is present), 2) absence of distinct repeating P waves, and 3) irregular atrial activity.

Hemodynamic consequences of AF can result from a variable combination of suboptimal ventricular rate control (either too rapid or too slow), loss of coordinated atrial contraction, beat-to-beat variability in

ventricular filling, and sympathetic activation (45-47). Consequences for individual patients vary, ranging from no symptoms to fatigue, palpitations, dyspnea, hypotension, syncope, or HF (48). The most common symptom of AF is fatigue. The appearance of AF is often associated with exacerbation of underlying heart disease, either because AF is a cause or consequence of deterioration, or because it contributes directly to deterioration (49, 50). For example, initially asymptomatic patients may develop tachycardia-induced ventricular dysfunction and HF (tachycardia-induced cardiomyopathy) when the ventricular rate is not adequately controlled (51, 52). AF also confers an increased risk of stroke and/or peripheral thromboembolism owing to the formation of atrial thrombi, usually in the left atrial appendage (LAA).

In the absence of an accessory AV pathway, the ventricular rate is determined by the conduction and refractory properties of the AV node and the sequence of wave fronts entering the AV node (53-55). L-type calcium channels are responsible for the major depolarizing current in AV nodal cells. Beta-adrenergic receptor stimulation enhances AV nodal conduction, whereas vagal stimulation (muscarinic receptor activation by acetylcholine) impedes AV nodal conduction (55). Sympathetic activation and vagal withdrawal such as with exertion or illness, accelerates the ventricular rate. Each atrial excitation wave front that depolarizes AV nodal tissue renders those cells refractory for a period of time, preventing successive impulses from propagating in the node—an effect called concealed conduction (55). This effect of concealed conduction into the AV node explains why the ventricular rate can be faster and more difficult to slow when fewer atrial wave fronts are entering the AV node, as in atrial flutter, compared to AF (53).

Loss of atrial contraction may markedly decrease cardiac output, particularly when diastolic ventricular filling is impaired by mitral stenosis, hypertension, hypertrophic cardiomyopathy (HCM), or restrictive cardiomyopathy (50, 56, 57). After restoration of sinus rhythm, atrial mechanical function fails to recover in some patients, likely as a consequence of remodeling or underlying atrial disease and duration of AF (58). Ventricular contractility is not constant during AF because of variable diastolic filling time and changes in the force-interval relationship (59, 60). Overall, cardiac output may decrease and filling pressures may increase compared to a regular rhythm at the same mean rate. In patients undergoing AV nodal ablation, irregular right ventricular (RV) pacing at the same rate as regular ventricular pacing resulted in a 15% reduction in cardiac output (60). Irregular R-R intervals also promote sympathetic activation (45, 46).

2.1.1. AF—Classification

AF may be described in terms of the duration of episodes and using a simplified scheme revised from the 2006 AF full-revision guideline, which is given in Table 4 (28, 30). Implanted loop recorders, pacemakers, and defibrillators offer the possibility of reporting frequency, rate, and duration of abnormal atrial rhythms, including AF (61, 62). Episodes often increase in frequency and duration over time.

Table 4. AF Definitions: A Simplified Scheme

Term	Definition

Paroxysmal AF	• AF that terminates spontaneously or with intervention within 7 d of onset. • Episodes may recur with variable frequency.
Persistent AF	• Continuous AF that is sustained >7 d.
Longstanding persistent AF	• Continuous AF of >12 mo duration.
Permanent AF	• Permanent AF is used when there has been a joint decision by the patient and clinician to cease further attempts to restore and/or maintain sinus rhythm. • Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of the AF. • Acceptance of AF may change as symptoms, the efficacy of therapeutic interventions, and patient and clinician preferences evolve.
Nonvalvular AF	• AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

AF indicates atrial fibrillation.

The characterization of patients with AF by the duration of their AF episodes (Table 4) has clinical relevance in that outcomes of therapy, such as catheter ablation, are better for paroxysmal AF than for persistent AF (28). When sinus rhythm is restored by cardioversion, however, the ultimate duration of the AF episode(s) is not known. Furthermore, both paroxysmal and persistent AF may occur in a single individual.

"Lone AF" is a historical descriptor that has been variably applied to younger individuals without clinical or echocardiographic evidence of cardiopulmonary disease, hypertension, or diabetes mellitus (63). Because definitions are variable, the term "lone AF'" is potentially confusing and should not be used to guide therapeutic decisions.

2.1.1.1. Associated Arrhythmias

Other atrial arrhythmias are often encountered in patients with AF. Atrial tachycardias are characterized by an atrial rate of ≥100 bpm with discrete P waves and atrial activation sequences. Atrial activation is most commonly the same from beat to beat.

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

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

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

Typical atrial flutter is a macro–re-entrant atrial tachycardia that usually proceeds up the atrial septum, down the lateral atrial wall, and through the cavotricuspid (subeustachian) isthmus between the tricuspid valve annulus and inferior vena cava, where it is commonly targeted for ablation. It is also known as "common atrial

flutter" or "cavotricuspid isthmus-dependent atrial flutter" (64). This sequence of activation (also referred to as "counterclockwise atrial flutter") produces predominantly negative "saw tooth" flutter waves in ECG leads II, III, and aVF, and a positive deflection in V1 (Figure 1). The atrial rate is typically 240 bpm to 300 bpm, but conduction delays in the atrial circuit due to scars from prior ablation, surgery, or antiarrhythmic drugs, can slow the rate to <150 bpm in some patients (65). When the circuit revolves in the opposite direction, flutter waves typically appear positive in the inferior ECG leads and negative in V1 (reverse typical atrial flutter, also referred to as "clockwise typical atrial flutter") (65). Unusual flutter wave morphologies occur in the presence of substantial atrial disease, prior surgery, or radiofrequency catheter ablation; the P-wave morphology is not a reliable indicator of the type of macro–re-entrant atrial tachycardia in these situations (70-72). Atrial flutter is often a persistent rhythm that requires electrical cardioversion or radiofrequency catheter ablation for termination. It is often initiated by a brief episode of atrial tachycardia or by AF (69, 73). This relationship between AF and atrial flutter may explain why ≥80% of patients who undergo radiofrequency catheter ablation of typical atrial flutter will have AF within the following 5 years (74).

AF may be misdiagnosed as atrial flutter when AF activity is prominent on ECG (75, 76). Atrial flutter may also arise during treatment with antiarrhythmic agents prescribed to prevent recurrent AF (77), particularly sodium channel blocking antiarrhythmic drugs such as flecainide or propafenone. Catheter ablation of the cavotricuspid isthmus is effective for prevention of recurrent atrial flutter in these patients while allowing continued antiarrhythmic treatment to prevent recurrent AF (78).

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

Figure 1. Atrial Tachycardias

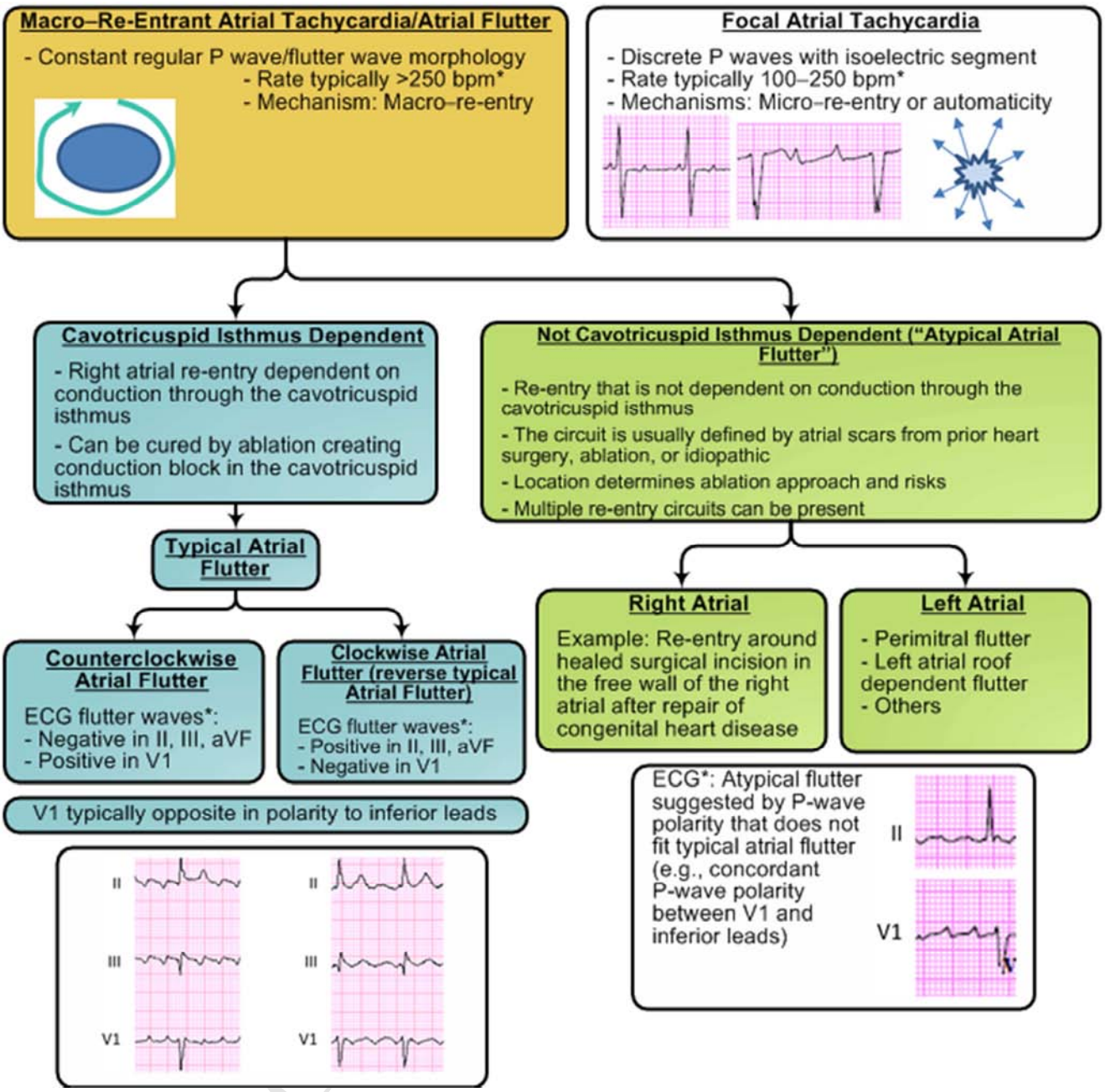


Diagram summarizing types of atrial tachycardias often encountered in patients with a history of AF, including those seen after catheter or surgical ablation procedures. P-wave morphologies are shown for common types of atrial flutter; however, the P-wave morphology is not always a reliable guide to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

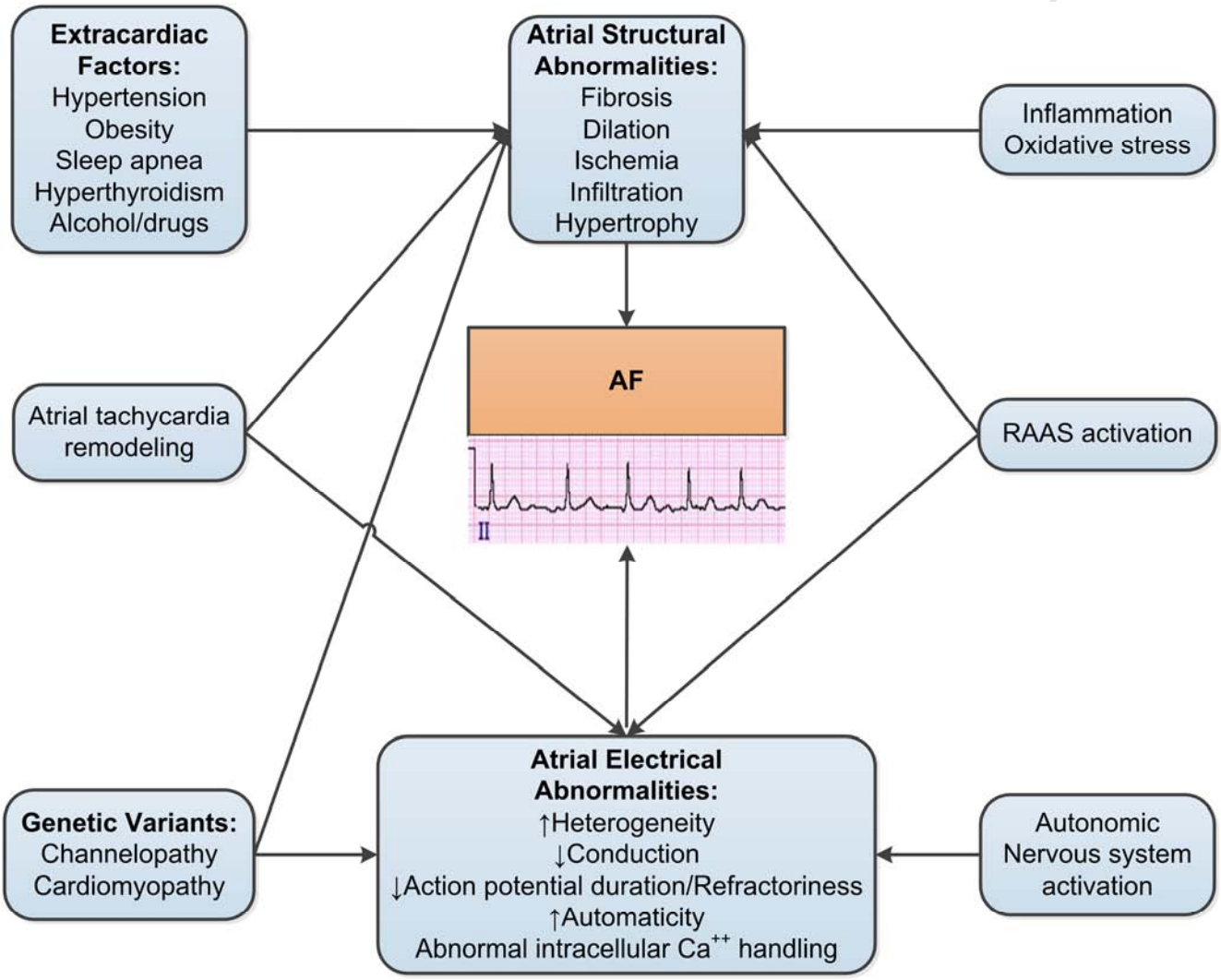
AF indicates atrial fibrillation and ECG, electrocardiogram (72, 80).

2.2. Mechanisms of AF and Pathophysiology

AF occurs when structural and/or electrophysiologic abnormalities alter atrial tissue to promote abnormal impulse formation and/or propagation (Figure 2). These abnormalities are caused by diverse pathophysiologic

mechanisms (28, 81, 82), such that AF represents a final common phenotype for multiple disease pathways and mechanisms that are incompletely understood.

Figure 2. Mechanisms of AF



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

2.2.1. Atrial Structural Abnormalities

Any disturbance of atrial architecture potentially increases susceptibility to AF (83). Such changes (e.g., inflammation, fibrosis, hypertrophy) occur most commonly in the setting of underlying heart disease associated with hypertension, coronary artery disease (CAD), valvular heart disease, cardiomyopathies, and HF which tend to increase LA pressure, cause atrial dilation, and alter wall stress. Similarly, atrial ischemia from CAD and infiltrative diseases such as amyloidosis, hemochromatosis, and sarcoidosis, can also promote AF. Additional promoters include extracardiac factors such as hypertension, sleep apnea, obesity, alcohol/drugs, and hyperthyroidism, which have pathophysiologic effects on atrial cellular structure and/or function. Even in patients with paroxysmal AF without recognized structural heart disease, atrial biopsies have revealed

inflammatory infiltrates consistent with myocarditis and fibrosis (84). In addition, prolonged rapid atrial pacing increases arrhythmia susceptibility and forms the basis for a well-studied model of AF. In the atria of patients with established AF and of animals subjected to rapid atrial pacing, there is evidence of myocyte loss from glycogen deposits and of mitochondrial disturbances and gap-junction abnormalities that cause cell necrosis and apoptosis (85-87). These structural abnormalities can heterogeneously alter impulse conduction and/or refractoriness, generating an arrhythmogenic substrate.

A common feature of both experimental and human AF is myocardial fibrosis (88). The atria are more sensitive to profibrotic signaling and harbor a greater number of fibroblasts than the ventricles. Atrial stretch activates the renin-angiotensin-aldosterone system, which generates multiple downstream profibrotic factors, including transforming growth factor-beta$_1$. Additional mechanisms, including inflammation and genetic factors, can also promote atrial fibrosis. The canine rapid ventricular pacing model of HF causes extensive atrial fibrosis and increases AF susceptibility (89). Fibrosis also occurs in the rapid atrial pacing model of AF. Late gadolinium-enhancement magnetic resonance imaging is used to image and quantitate atrial fibrosis noninvasively (90-95). Human studies show a strong correlation between regions of low voltage on electro-anatomic mapping and areas of late enhancement on magnetic resonance imaging. Preliminary results suggest that the severity of atrial fibrosis correlates with the risk of stroke (91) and decreased response to catheter ablation (90).

2.2.2. Electrophysiologic Mechanisms

AF requires both a trigger for initiation and an appropriate anatomic substrate for maintenance, both of which are potential targets for therapy. Several hypotheses have been proposed to explain the electrophysiologic mechanisms that initiate and maintain AF (28). In humans, the situation is complex, and it is likely that multiple mechanisms coexist in an individual patient.

2.2.2.1. Triggers of AF

Ectopic focal discharges often initiate AF (96-98). Rapidly firing foci initiating paroxysmal AF arise most commonly from LA myocardial sleeves that extend into the pulmonary veins. These observations led to the development of pulmonary vein isolation as the cornerstone for radiofrequency catheter ablation strategies (28). Unique anatomic and electrophysiologic features of the pulmonary veins and atriopulmonary vein junctions may account for their arrhythmogenic nature. Atrial myocardial fibers are oriented in disparate directions around the pulmonary veins and the posterior LA, with considerable anatomic variability among individuals. Conduction abnormalities that promote re-entry are likely due to relatively depolarized resting potentials in pulmonary vein myocytes that promote sodium channel inactivation and to the abrupt changes in fiber orientation. Re-entry is further favored by abbreviated action potentials and refractoriness in pulmonary vein myocytes (99). Isolated pulmonary vein myocytes also demonstrate abnormal automaticity and triggered activity that could promote rapid focal firing. Additional potential sources for abnormal activity include interstitial cells (similar to pacemaker cells in the gastrointestinal tract) (100) and melanocytes (101), both of which have been identified in

pulmonary veins. Although the pulmonary veins are the most common sites for ectopic focal triggers, triggers can also arise elsewhere, including the posterior LA, ligament of Marshall, coronary sinus, venae cavae, septum, and appendages.

Abnormal intracellular calcium handling may also play a role in AF owing to diastolic calcium leak from the sarcoplasmic reticulum, which can trigger delayed after depolarizations (102-106).

2.2.2.2. Maintenance of AF

Theories proposed to explain the perpetuation and maintenance of AF include 1) multiple independent re-entrant wavelets associated with heterogeneous conduction and refractoriness; 2) ≥1 rapidly firing foci, which may be responsive to activity from cardiac ganglion plexi; and 3) ≥1 rotors, or spiral wave re-entrant circuits (28, 82, 88, 107-113). With a single rapid focus or rotor excitation, wave fronts may encounter refractory tissue and break up during propagation, resulting in irregular or fibrillatory conduction (28, 107, 110). Both rapid focal firing and re-entry may be operative during AF.

These presumed mechanisms have driven the development of therapies. The atrial maze procedure and ablation lines may interrupt paths for multiple wavelets and spiral re-entry. Using a biatrial phase mapping approach, a limited number of localized, rapid drivers (mean of approximately 2 per patient) were identified in a small group of patients with various types of AF (112). In most cases, these localized sources appeared to be re-entrant, while in others they were consistent with focal triggers and radiofrequency catheter ablation targeting of these sites often terminated or slowed AF. Other investigators, using a noninvasive continuous biatrial mapping system, report contrasting results, observing mostly evidence for multiple wavelets and focal sites rather than rotor activity (114).

Some investigators targeted regions in which electrogram recordings show rapid complex atrial fractionated electrograms, which are felt to be indicative of the substrate for AF or markers for ganglion plexi (see Section 2.2.2.3. for ablation of AF) (109). The relation of complex atrial fractionated electrograms to AF remains controversial.

2.2.2.3. Role of the Autonomic Nervous System

Autonomic stimulation can provoke AF (28, 98, 115). Activation of the parasympathetic and/or sympathetic limbs can provoke atrial arrhythmias (108, 116). Acetylcholine activates a specific potassium current, $I_{K,ACh}$, that heterogeneously shortens atrial action potential duration and refractoriness, increasing susceptibility to re-entry. Sympathetic stimulation increases intracellular calcium, which promotes automaticity and triggered activity. Increased parasympathetic and/or sympathetic activity prior to onset of AF has been observed in some animal models and humans (117, 118).

Plexi of autonomic ganglia that constitute the intrinsic cardiac autonomic nervous system are located in epicardial fat near the pulmonary vein-LA junctions and the ligament of Marshall. Stimulation of the ganglia in animals elicits repetitive bursts of rapid atrial activity. These plexi are often located in proximity to atrial sites

where complex atrial fractionated electrograms are recorded. Ablation targeting these regions improved outcomes over pulmonary vein isolation alone in some but not all studies (119-121).

In some patients with structurally normal hearts, AF is precipitated during conditions of high-parasympathetic tone, such as during sleep and following meals, and is referred to as "vagally mediated AF" (122). Avoidance of drugs, such as digoxin, that enhance parasympathetic tone has been suggested in these patients, but this remains an unproven hypothesis. Catheter ablation targeting ganglion plexi involved in vagal responses abolished AF in only 2 of 7 patients in 1 small series (120). Adrenergic stimulation, as during exercise, can also provoke AF in some patients (123).

2.2.3. Pathophysiologic Mechanisms

2.2.3.1. Atrial Tachycardia Remodeling

AF often progresses from paroxysmal to persistent over a variable period of time. Cardioversion of AF and subsequent maintenance of sinus rhythm are more likely to be successful when AF duration is <6 months (124). The progressive nature of AF is consistent with studies demonstrating that AF causes electrical and structural remodeling such that "AF begets AF" (125, 126).

2.2.3.2. Inflammation and Oxidative Stress

Inflammation (e.g., associated with pericarditis and cardiac surgery), may be linked to AF and can be correlated with a rise in plasma concentrations of C-reactive protein (81). Inflammatory infiltrates consistent with myocarditis are often present in the atria of patients with AF and in animals with atrial dilation. Plasma concentrations of C-reactive protein and interleukin-6 are elevated in AF; increased C-reactive protein predicts the development of AF and relapse after cardioversion; and genetic variants in the interleukin-6 promoter region may influence the development of postoperative AF. In the canine pericarditis and atrial tachypacing models, prednisone suppresses AF susceptibility and reduces plasma concentrations of C-reactive protein (127).

Aging, environmental stress, inflammation, and activation of the renin-angiotensin-aldosterone system can cause oxidative damage in the atrium. Oxidative changes are present in the atrial tissue of patients with AF and are associated with upregulation of genes involved in the production of reactive oxygen species. In human AF and a porcine model of atrial tachypacing, atrial superoxide production increased, with an apparent contribution of NAD(P)H oxidase (128). The antioxidant ascorbate attenuated electrical remodeling in the canine atrial tachypacing model and reduced postoperative AF in a small study in humans (129).

2.2.3.3. The Renin-Angiotensin-Aldosterone System

Stimulation of the renin-angiotensin-aldosterone system promotes structural and likely electrophysiologic effects in the atrium and ventricle that increase arrhythmia susceptibility (130-133). In addition to adverse hemodynamic effects, activation of multiple cell signaling cascades promotes increased intracellular calcium, hypertrophy, apoptosis, cytokine release and inflammation, oxidative stress, and production of growth-related factors that also stimulate fibrosis, as well as possible modulation of ion channel and gap-junction dynamics.

Components of the renin-angiotensin-aldosterone system (including angiotensin II, angiotensin-converting enzyme [ACE], and aldosterone) are synthesized locally in the atrial myocardium and are increased during atrial tachypacing and AF. Variants in the ACE gene that increase angiotensin II plasma concentrations can elevate risk of AF, while selective cardiac overexpression of ACEs causes atrial dilation, fibrosis, and increased susceptibility of AF. Therapy with these agents can reduce the occurrence of AF in patients with hypertension or left ventricular (LV) dysfunction but does not help prevent recurrence of AF in the absence of these other indications for these drugs (Section 6.2.1).

Aldosterone plays an important role in angiotensin II-mediated inflammation and fibrosis; in patients with primary hyperaldosteronism, the incidence of AF is increased. In experimental models of HF, spironolactone and eplerenone decreased atrial fibrosis and/or susceptibility of AF. Eplerenone therapy is associated with decreased AF in patients with HF (134).

2.2.3.4. Risk Factors and Associated Heart Disease

Multiple clinical risk factors, electrocardiographic and echocardiographic features, and biochemical makers are associated with an increased risk of AF (Table 5). One epidemiologic analysis found that 56% of the population-attributable risk of AF could be explained by ≥1 common risk factor (135). Thus, it may be possible to prevent some cases of AF through risk factor modification such as blood pressure control or weight loss.

Many potentially "reversible" causes of AF have been reported, including binge drinking, cardiothoracic and noncardiac surgery, myocardial infarction (MI), pericarditis, myocarditis, hyperthyroidism, electrocution, pneumonia, and pulmonary embolism (10, 49, 136-138). AF that occurs in the setting of Wolff-Parkinson-White (WPW) syndrome, AV nodal re-entrant tachycardia, or atrial ectopic tachycardia may resolve after catheter ablation for these arrhythmias (69). It is important to recognize that there are few data to support the notion that patients with AF that occurs in the setting of 1 of these potentially "reversible" conditions are, in fact, cured of AF after effective treatment or elimination of the condition. Since long-term follow-up data are not available in these clinical scenarios and AF may recur, these patients should receive careful follow-up.

Table 5. Selected Risk Factors and Biomarkers for AF

Clinical Risk Factors	References
Increasing age	(139)
Hypertension	(139)
Diabetes mellitus	(139)
MI	(139)
VHD	(139)
HF	(38, 139)
Obesity	(140-142)
Obstructive sleep apnea	(142)
Cardiothoracic surgery	(137)
Smoking	(143)
Exercise	(144-146)
Alcohol use	(147-149)
Hyperthyroidism	(150-152)

Increased pulse pressure	(153)
European ancestry	(154)
Family history	(155)
Genetic variants	(156-159)
Electrocardiographic	
LVH	(35)
Echocardiographic	
LA enlargement	(35, 160)
Decreased LV fractional shortening	(35)
Increased LV wall thickness	(35)
Biomarkers	
Increased CRP	(86, 161)
Increased BNP	(162, 163)

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

See Online Data Supplements 1 and 2 for additional data on electrophysiologic and pathophysiologic mechanisms (http://jaccjacc.cardiosource.com/DataSupp/MASTER_2014_AF_Evidence_Table_Supplement_03182014.pdf).

3. Clinical Evaluation: Recommendation

Class I

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

The diagnosis of AF in a patient is based on the patient's clinical history and physical examination and is confirmed by ECG, ambulatory rhythm monitoring (e.g., telemetry, Holter monitor, event recorders), implanted loop recorders, pacemakers or defibrillators, or, in rare cases, by electrophysiological study. The clinical evaluations, including additional studies that may be required, are summarized in Appendix 4.

3.1. Basic Evaluation of the Patient With AF

3.1.1. Clinical History and Physical Examination

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

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

abnormalities. The pulse in atrial flutter is often regular and rapid, and venous oscillations may be visible in the jugular pulse.

3.1.2. Investigations

An ECG, or other electrocardiographic recording, is the essential tool for confirming AF. A chest radiograph should be done if pulmonary disease or HF is suspected and may also detect enlargement of the cardiac chambers. As part of the initial evaluation, all patients with AF should have a 2-dimensional transthoracic echocardiogram to detect underlying structural heart disease, assess cardiac function, and evaluate atrial size. Additional laboratory evaluation should include assessment of serum electrolytes; thyroid, renal, and hepatic function; and a blood count.

Transesophageal Echocardiography (TEE): TEE is the most sensitive and specific technique to detect LA thrombi as a potential source of systemic embolism in AF and can be used to guide the timing of cardioversion or catheter ablation procedures (Section 6.1.1). TEE can also identify features associated with an increased risk of LA thrombus formation, including reduced LAA flow velocity, spontaneous LA contrast, and aortic atheroma. In 5% to 15% of patients with AF, a TEE before planned cardioversion revealed a LA or LAA thrombus (164, 165).

Electrophysiological Study: An electrophysiological study can be helpful when initiation of AF is due to a supraventricular tachycardia, such as AV node re-entrant tachycardia, AV re-entry involving an accessory pathway, or ectopic atrial tachycardia. Ablation of the supraventricular tachycardia may prevent or reduce recurrences of AF. Electrophysiological study is often warranted in patients with a delta wave on the surface ECG indicating pre-excitation. Some patients with AF also have atrial flutter that may benefit from treatment with radiofrequency catheter ablation. AF associated with rapid ventricular rates and a wide-complex QRS (aberrant conduction) may sometimes be mislabeled as ventricular tachycardia, and an electrophysiological study can help establish the correct diagnosis.

Additional Investigation of Selected Patients With AF: Plasma levels of B-type natriuretic peptide or N-terminal pro- B-type natriuretic peptide may be elevated in patients with paroxysmal and persistent AF in the absence of clinical HF, and levels decrease rapidly after restoration of sinus rhythm. A sleep study may be useful if sleep apnea is suspected (166).

3.1.3. Rhythm Monitoring and Stress Testing

Prolonged or frequent monitoring may be necessary to reveal episodes of asymptomatic AF. ECG, ambulatory rhythm monitoring (e.g., telemetry, Holter monitor, and event recorders), and exercise testing can be useful to judge the adequacy of rate control. Patient-activated ECG event recorders can help assess the relation to symptoms, whereas auto-triggered event recorders may detect asymptomatic episodes. These technologies may also provide valuable information to guide drug dosage for rate control or rhythm management.