Diagnostic Evaluation and Follow-Up of Patients with Atrial Fibrillation

Patrick Dillon, MD, Hamid Ghanbari, MD*

KEYWORDS

• Atrial fibrillation • Diagnostic evaluation • Follow-up • Risk factors • Symptoms • Quality of life

KEY POINTS

- Atrial fibrillation (AF) is the most common clinically encountered cardiac arrhythmia.
- AF carries significant morbidity and mortality.
- As the prevalence of AF continues to increase, so too will the number of both outpatient and inpatient visits that are either directly or indirectly attributable to the condition.
- Clinicians across many specialties will likely face diagnostic and therapeutic challenges associated with AF more frequently in the coming years and decades.

INTRODUCTION

Atrial fibrillation (AF) is the most common clinically encountered cardiac arrhythmia. The estimated number of patients with AF in the United States is estimated to be between 3 and 6 million.[1] The prevalence of AF is highest in the elderly, and it has been estimated that 4 of 5 patients with AF are 65 years of age or older.[2] Over the next 2 to 3 decades, the incidence is expected to increase to 2.6 million, and the prevalence may increase to more than 12 million.[3]

AF carries with it significant morbidity and mortality. It is an important risk factor for ischemic stroke, and as many as 15% of strokes have been attributed to AF.[4,5] It has also been associated with heart failure, decreased functional status, dementia, lower quality of life, and death.[6–11] As the prevalence of AF continues to increase, so too will the number of both outpatient and inpatient visits that are either directly or indirectly attributable to the condition. Therefore, clinicians across many specialties will likely face diagnostic and therapeutic challenges associated with AF more frequently in the coming years and decades.

In this review, the diagnostic evaluation and considerations for follow up after the initial diagnosis of AF are discussed. Signs and symptoms, medical history, and physical examination findings useful when evaluating patients at the bedside are highlighted, and diagnostic approaches in varying clinical scenarios are discussed. Important considerations for both short-term and long-term outpatient follow-up are also reviewed.

DIAGNOSTIC EVALUATION

Clinical History

Symptoms

Most patients with AF report symptoms attributable to AF. There are many symptoms related to AF; however, there is significant interindividual and intraindividual variability. The most common symptoms that prompt patients with previously undiagnosed AF to pursue evaluation include palpitations, dyspnea, chest pain, fatigue, and

Disclosures: None.
Division of Cardiovascular Medicine, University of Michigan Health System, 1500 East Medical Center Drive, Ann Arbor, MI 48109, USA
* Corresponding author.
E-mail address: ghhamid@med.umich.edu

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syncope (Fig. 1).[12,13] Palpitations are an unpleasant awareness of the forceful, rapid, or irregular beating of the heart. In a prospective observational study,[12] more than half of patients with AF reported experiencing palpitations. When further subdivided, 79% of patients with paroxysmal and 45% of patients with chronic AF experienced palpitations. The most common precipitating factors were exercise, emotion, postprandial state, and caffeine.

Up to 40% to 50% of patients with AF report dyspnea. The underlying cause of shortness of breath may be difficult to assess, however, because many conditions that cause dyspnea also predispose to AF, like chronic obstructive pulmonary disease (COPD), structural heart disease, and obstructive sleep apnea (OSA).[12,14] Dyspnea related to AF can result in a decline in performance status. The presence of AF, for example, has been shown to be associated with higher New York Heart Association functional class.[15] Furthermore, patients with AF were found to have significantly lower exercise performance compared with similar patients in whom sinus rhythm was restored and maintained.[16]

Chest pain is frequently associated with AF. Fast heart rates, irregular ventricular response, and loss of atrial contraction may lead to a decrease in cardiac output, which contributes to ischemic chest pain in patients with coronary artery disease. Chest pain is seen in patients with AF despite the absence of coronary artery disease, and impaired microvascular flow is a possible explanation.[17,18] Symptoms like lightheadedness and syncope are more likely to be seen in patients with structural heart disease, and although clinically important, they occur less frequently than symptoms described earlier.[19]

Although many patients experience symptoms related to AF, observed frequencies of symptoms may be overestimated, because asymptomatic patients often do not present for evaluation. Several studies have reported that between 10% and 20% of patients with AF are asymptomatic.[12,20–22] One observational study found that patients without symptoms were significantly more likely to be male, carry a diagnosis of diabetes, have a larger left atrial size, have a lower resting heart rate, and have progressed to persistent or permanent AF by the time of AF diagnosis.[22] Furthermore, although $CHADS_2$ and CHA_2DS_2-VASc scores were similar for symptomatic and asymptomatic patients, asymptomatic patients were less likely to be diagnosed with AF and subsequently treated with anticoagulation. An observational study found that 20% of patients with cryptogenic stroke were given a diagnosis of AF during follow-up after wearing a 30-day event monitor.[23]

Quality of life

Quality of life is significantly reduced in most patients with AF.[24,25] Improvements in symptoms and health-related quality of life (HRQOL) are

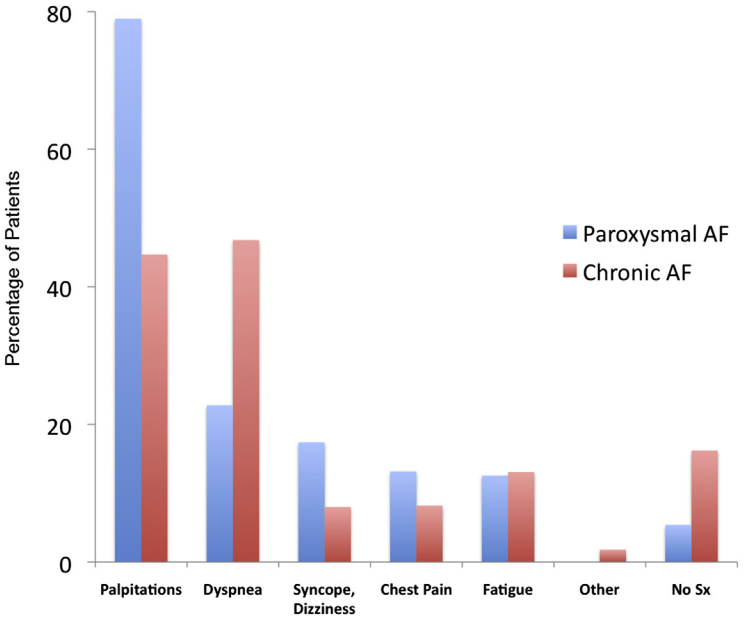

Fig. 1. Frequency of reported symptoms for paroxysmal AF and chronic AF. Sx, symptoms. (*Data from* Levy S, Maarek M, Coumel P, et al. Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. The College of French Cardiologists. Circulation 1999;99:3028–35.)

important therapeutic goals in management of patients with AF, along with reducing the risk of stroke, mortality, and cardiovascular morbidity.[19] There have been several global and disease-specific HRQOL measures that have been used in patients with AF. The most commonly used global HRQOL tools in patients with AF are SF-36, SF-12, EuroQOL, and EQ-5D.

The SF-36 is the most widely used generic HRQOL instrument used in patients with AF. It has been validated in many studies evaluating HRQOL in cardiac and noncardiac conditions. It consists of a 36-item questionnaire, which assesses 8 health domains. These domains include general health perception, physical functioning, social functioning, vitality, bodily pain, mental health, and role limitations caused by emotional and physical problems.[26] It also generates psychometrically based physical and mental component summary scores.[26] The SF-12 is a shorter version of SF-36, which uses 12 questions to measure HRQOL.[27] The physical and mental component summary scores from the SF-12 mirror those from the SF-36.[27] The EuroQOL is focused on 5 health domains: mobility, self-care, usual activities, pain/discomfort, and anxiety or depression.[28] It also has the advantage of the EQ-5D method, which can transform raw scores to preference-based utility weights.[29]

The advantage of these global instruments to assess AF-related HRQOL is their long validation track record, generalizability, and large data available from the population with AF. However, these measures, which reflect general health and functioning and scores among patients with AF, are strongly influenced by patient demographics and comorbid conditions.[30] Therefore, these instruments are less sensitive to change, particularly in patients with multiple medical conditions.

The Arrhythmia Symptom Checklist is the most commonly used cardiac questionnaire used in the assessment of HRQOL in patients with AF. It rates the frequency (0–4) and severity (1–3) of 16 symptoms commonly associated with AF.[31] It is easy to use and sensitive to change. However, the symptoms assessed are nonspecific, and it does not assess functional status and patient satisfaction. These factors limit its applicability as a stand-alone HRQOL measure in AF.

More recently, there has been an emphasis on developing several instruments specific to assessment of HRQOL in patients with AF. The Atrial Fibrillation Symptom Score (AFSS) is a 19-item disease-specific measure of quality of life in AF. It includes questions regarding AF-related symptoms, health care use, frequency, overall severity, and duration of symptomatic AF episodes.[16,32,33] The AF symptom score can be calculated using the AFSS summary score. The AFEQT (Atrial Fibrillation Effect on Quality-of-life) questionnaire is a 20-item instrument designed to assess HRQOL in AF. It assesses 4 health domains: symptoms, activities, treatment concerns, and satisfaction. A summary score is generated based on the first 3 health domains. The responses are shown as a 7-point Likert scale. Patients are asked to indicate the impact of AF on their health status in the previous 4 weeks. The raw scores from each domain are transformed to a 0 to 100 scale, on which a score of 0 indicates the most severe symptoms and score of 100 indicates no limitations.

Assessing symptoms in AF can be challenging, and these instruments are complex and require significant time to complete. This factor has limited their wide clinical adaptation. The Canadian Cardiovascular Society Severity of Atrial Fibrillation (CCS-SAF) scale was created as a concise, symptom-based severity scale intended for routine clinical use in patients with AF.[34] The CCS-SAF scale provides a potentially clinically useful scale for practitioners to assess patient status and to communicate the severity of the functional consequences of the patient's symptoms from AF. It closely approximates patient-reported subjective measures of quality of life in AF and may be practical for clinical use.[32] The Severity of Atrial Fibrillation (SAF) class, derived from CCS-SAF, is imperfectly correlated to generic quality of life measures in the SF-36 and AFSS. This situation presumably occurs because the SAF scale captures, by design, all components of the AF syndrome (including, eg, symptom severity during AF, adverse effects of treatment administered, and the physical and psychological consequences of the disease state), whereas the generic quality of life measures capture only components of the AF illness burden.[32]

Most data focused on assessing HRQOL in patients with AF are derived from intervention studies assessing rate and rhythm control strategies. These studies included patients with highly symptomatic AF with baseline HRQOL scores, which were significantly lower than the general population.[16,25,33,35–37] Studies including less selected patients with AF have also confirmed that most patients with AF have lower HRQOL compared with the general population. In a cross-sectional evaluation of 142 patients (mean age 58 years),[24] patients with AF had significantly worse scores compared with healthy controls. In a cohort of 963 patients included in the FRACTAL (Fibrillation Registry Assessing Costs, Therapies, Adverse Events and Lifestyle) registry,[30] the HRQOL scores were significantly lower than healthy controls.

The baseline comorbid conditions, age, and gender affect HRQOL in patients with AF. This situation is influenced by the use of generic HRQOL instruments, which are affected by age and underlying medical conditions. The severity of heart failure symptoms, chronic pulmonary disease, valvular heart disease, and coronary artery disease has been associated with lower HRQOL in patients with AF.[33,38] Personality traits may also play an important role in perceived HRQOL. Depression, pessimism, and personality traits relating to the response to physical and emotional stressors (anxiety sensitivity and somatization) have been associated with diminished HRQOL in patients with AF.[39,40] Gender plays an important role in HRQOL in patients with AF. Women report a lower HRQOL and greater symptom burden than men.[38,41,42] Older patients report lower symptom burden associated with AF when compared with younger patients.[38] They also tend to have a different symptom pattern, with fatigue and dyspnea being more prominent in the elderly, whereas palpitations are more prominent in younger patients.[38] HRQOL may not be significantly affected in some patients, in particular, the elderly. In a study of 52 patients (mean age 77 years) with chronic AF,[43] there were no observed differences in HRQOL and exercise tolerance compared with age-matched control individuals without AF. Therefore the segment of the population with AF studied influences the impact of AF on HRQOL.

Past medical history

Many conditions predispose to the development of AF, and several risk factors have been established (**Box 1**). Age is an independent risk factor for AF, and every additional decade of life for men and women nearly doubles the risk of developing AF.[2,44] Independent cardiovascular risk factors include hypertension, valve disease, congestive heart failure, and myocardial infarction.[44] A systolic blood pressure higher than 150 mm Hg has been shown to be a statistically significant risk factor for incident AF.[45] As a surrogate of systolic hypertension and aortic stiffness, a widened pulse pressure is a risk for AF, with an adjusted hazard ratio of 1.26 per 20 mm Hg increase in blood pressure.[46]

Although the causal relationship between heart failure and AF is poorly understood, both conditions share common risk factors. The odds ratio of AF for heart failure was 4.5 for men and 5.9 for women in the Framingham Heart Study.[44,47] Increased frequency of AF has been described in the setting of acute coronary syndrome and prevalent myocardial infarction, with an incidence between 6% and 21% during acute myocardial infarction.[48] In addition, perhaps the most commonly discussed risk factor is valvular heart disease. Left-sided valvular lesions have been more thoroughly studied than right-sided lesions, and specifically, mitral stenosis and mitral regurgitation. One observational study found that by the time of clinical presentation, 20% of patients with mitral stenosis had already developed AF, and 33% had developed AF by the end of the 10-year follow-up period.[49] Incident AF in degenerative mitral regurgitation caused by flail leaflet was 18% and 48% at 5 and 10 years, respectively, and rates were similar for mitral regurgitation caused by mitral valve prolapse.[50]

AF is a well-recognized manifestation of hyperthyroidism, with a greater than 2-fold increase in risk.[51] In the Canadian Registry for Atrial Fibrillation and Danish National Registry, overt hyperthyroidism was observed in 1% and 8.3% of patients with AF, respectively.[21,52] In addition, patients with subclinical hyperthyroidism as well as patients with thyroid-stimulating hormone levels in the high-normal range have been observed to be at increased risk for AF.[53,54] In contrast, there is not a significant association between AF and hypothyroidism.[55]

Diabetes and metabolic syndrome are independent risk factors for incident AF.[44,56] Accordingly, obesity has been found to predispose to AF, with adjusted hazard ratios of 1.52 and 1.46 for men and women, respectively.[57] In addition, because obesity is a risk factor for OSA, the prevalence of OSA is significantly higher in patients with AF

Box 1
Independent risk factors for development of AF

Risk factors for AF

- Age
- Hypertension
- Valvular heart disease
- Congestive heart failure
- Myocardial infarction
- Diabetes mellitus
- Obesity (body mass index [calculated as weight in kilograms divided by the square of height in meters] $\geq$30 kg/m^2)
- Obstructive sleep apnea
- Hyperthyroidism
- Cigarette smoking
- Heavy ethanol intake

compared with other cardiovascular diseases. It is an independent risk factor for AF in patients younger than 65 years.[58,59] Although these conditions are treatable and even preventable, they continue to increase in incidence and prevalence. Modifiable risk factors like smoking (and resultant COPD) and heavy alcohol use predispose to AF.[60–62]

Medications

A variety of medications have been identified as possible inciting and reversible underlying causes of AF. Generally, the development of AF results from a trigger, whereas the maintenance of AF requires a change in electrophysiologic substrate.[63] The underlying mechanisms of drug-induced AF affect either trigger or substrate and include (1) adrenergic or vagal stimulation, (2) modified atrial conduction, refractoriness, or automaticity, (3) direct cardiotoxicity, (4) coronary vasoconstriction, and (5) electrolyte disturbances.[64]

Adenosine is often used to terminate supraventricular tachycardia (SVT); however, it can induce AF in up to 10% of cases, although this is typically transient, because of the short half-life of adenosine.[65] Other cardiovascular medications that can incite AF include dopamine, dobutamine, and milrinone (by increasing adrenergic stimulation), anticholinergics (by increasing vagal stimulation), and thiazides (by causing electrolyte disturbances). Although digoxin is used for rate control of SVT or AF, toxic levels may lead to the development of atrial tachycardia or even AF.

Although it is difficult to describe a causal relationship between a drug and incident AF, it is important to review medicines when clinically evaluating patients with AF. Although a drug may not necessarily cause AF, it may potentiate tachycardia in the setting of established electrophysiologic substrate for AF. For example, patients with reactive airway disease (a risk factor for AF) may be given β-agonists like albuterol or salmeterol or they may be taking theophylline, a drug that carries increased risk for AF.[66]

PHYSICAL EXAMINATION

All patients with suspected or newly diagnosed AF should receive a complete examination of the cardiovascular system. Initial findings to suggest the presence of AF include an irregular pulse, irregular jugular venous pulsation, and variability in intensity of the first heart sound that occurs with variable ventricular preload. Further observation of the jugular venous pulsation shows an absent a-wave. Although a regular heart rhythm on examination may suggest a sinus rhythm, it is also found in patients with AF and complete heart block with a junctional or ventricular escape.

Special attention should be given to the presence of murmurs to suggest stenotic or regurgitant lesions, which may contribute to the development of AF. Loss of atrial contraction can lead to hypervolemia and heart failure. Furthermore, decompensation in heart failure status may be the underlying cause of AF. The initial examination to assess for hypervolemia can be important for prognosis, because the presence of increased jugular venous pulsation, peripheral edema, rales, or the presence of a third heart sound were all associated with higher cardiovascular mortality in patients with heart failure and AF.[67]

Diagnostics

An initial clinic visit for evaluation of suspected or documented AF typically includes an electrocardiogram (ECG) and a transthoracic echocardiogram (TTE). ECG may provide evidence of chamber enlargement or hypertrophy or previous myocardial infarction and establish a baseline corrected QT interval if antiarrhythmic medications are a consideration. TTE allows further characterization of valvular heart disease, systolic and diastolic function, chamber hypertrophy, and atrial size. Left atrial dilation suggests underlying electroanatomic remodeling, and identification of left atrial enlargement can guide management. For example, left atrial diameter less than 50 to 55 mm predicts a higher probability of successful catheter ablation of AF.[68] As described earlier, other diagnostics as guided by physical examination should include thyroid function tests, pulmonary function tests, and sleep study.

Advanced imaging modalities may offer more guidance for management decisions in the future. Three-dimensional echocardiography has been suggested to provide a more accurate assessment of left atrial volume when compared with standard two-dimensional echo.[69] If catheter ablation is being considered, cross-sectional imaging with computed tomography or cardiac magnetic resonance (MR) offers detailed information regarding pulmonary vein location and geometry. Furthermore, late gadolinium enhancement MR sequences used to characterize the extent of left atrial fibrosis can predict response to catheter ablation. Mild late gadolinium enhancement, when compared with extensive enhancement, is associated with lower rates of AF recurrence after catheter ablation.[70]

Ambulatory external ECG (AECG) monitoring offers the ability to diagnose clinically suspected paroxysmal AF. Short-term 24-hour to 48-hour

continuous monitors have the advantage of documenting AF regardless of patient symptoms but with a trade-off of low sensitivity because of the short duration of observation. Intermittent patient-activated, longer-term recorders increase sensitivity by allowing more time for patients to develop symptoms but fail to document asymptomatic episodes of paroxysmal AF. Newer-generation ambulatory telemetry monitors were developed to overcome limitations of short-term or patient-activated monitors; however, these require storage and review of large amounts of data.

AECG monitoring can also be particularly useful in patients with cryptogenic stroke. Longer-term observation of rhythm in patients with stroke of unclear cause more accurately diagnoses AF. In the EMBRACE trial,[71] patients with cryptogenic stroke or transient ischemic attack were randomly assigned to monitoring with either a 30-day event recorder or with standard 24-hour monitoring. Extended follow-up with 30-day event monitoring significantly improved detection of AF and diagnosed AF in 16% of patients compared with 3% of patients in the standard monitoring group. In another study,[72] longer-term monitoring with an insertable cardiac monitor after cryptogenic stroke diagnosed AF in 12% of patients at 1 year, compared with 2% of patients in the standard monitoring group.

FOLLOW-UP

Anticoagulation

The $CHADS_2$ score has been used for many years to guide anticoagulation therapy to mitigate stroke risk in patients with nonvalvular AF.[73] Guidelines from the European Society of Cardiology (ESC) and more recent guidelines from the American College of Cardiology (ACC), American Heart Association (AHA), and Heart Rhythm Society (HRS) recommend use of the CHA_2DS_2-VASc score for anticoagulation in nonvalvular AF.[74,75] A CHA_2DS_2-VASc score of 2 or higher warrants full anticoagulation for patients in whom it is not contraindicated. The ESC guidelines, more so than the ACC/AHA/HRS guidelines, lean toward no anticoagulation, as opposed to aspirin, in patients with CHA_2DS_2-VASc of zero and toward full anticoagulation, as opposed to aspirin, in patients with CHA_2DS_2-VASc of 1.

Warfarin, a vitamin K antagonist, interferes with γ-carboxylation of coagulation factors II, VII, IX, and X. Many clinics approach warfarin dosing as a 7-day week total dose divided into smaller daily doses. The international normalized ratio (INR) response should be monitored every 2 to 5 days after initiation of treatment until stable INR levels are documented on stable dosing, after which monitoring is typically performed every 4 weeks. A randomized trial[76] comparing classic clinic-based monthly INR monitoring with home-based weekly point-of-care INR monitoring for patients on warfarin because of mechanical heart valves or AF found no difference in time to first stroke, major bleeding episode, or death between the 2 groups. As user-friendly data-sharing platforms become more available in the health care industry, remote INR monitoring could present an alternative to the clinic-based model of INR monitoring.

Dabigatran, a direct thrombin inhibitor, as well as rivaroxaban and apixaban, activated factor Xa inhibitors, are 3 target-specific oral anticoagulants (TSOA) that have recently been approved by the US Food and Drug Administration for stroke risk mediation in nonvalvular AF.[77–79] The TSOA agents offer alternative anticoagulation treatment to warfarin, with the benefit of fixed dosing regimens and fewer drug-drug interactions. **Tables 1** and **2** compare their pharmacologic and risk profiles. Dabigatran is the most dependent on renal clearance, whereas apixaban is the least dependent. Drug levels increase with decreasing renal function and expose the patient to a higher risk of bleeding. Creatinine clearance calculation is recommended to guide dosing for dabigatran and rivaroxaban, whereas creatinine level is recommended for apixaban dosing. Renal function should be monitored frequently during treatment with TSOAs.

Antiarrhythmic Therapy

Although many studies have shown similar survival rates for rhythm control and rate control strategies,[36,80,81] rhythm control can often be the preferred management choice in patients with severe symptoms. **Fig. 2** and **Table 3** review the use of antiarrhythmic medications in different patient populations. Class IC agents should be avoided in patients with coronary artery disease or heart failure. Dronedarone and sotalol should also be avoided in patients with heart failure.

Amiodarone and ibutilide (available only as intravenous formulation) are commonly used class III agents for patients with recent onset paroxysmal AF in the acute care setting. Both agents have been shown to increase the efficacy of direct-current cardioversion if given before electrical treatment.[82,83]

The class IC agents, flecainide and propafenone, can be used both as a pill-in-the-pocket strategy for intermittent, symptomatic paroxysmal

Table 1
Comparison of warfarin with target-specific oral anticoagulants

	Warfarin	Dabigatran[a]	Rivaroxaban[b]	Apixaban[c]
Target of inhibition	Vitamin K	Thrombin	Factor Xa	Factor Xa
Studied dose (mg)	—	150 twice a day 110 twice a day	20 daily	5 twice a day
Approved dose (mg)	—	150 twice a day 75 twice a day (creatinine clearance 15–30 mL/min)	20 daily 15 daily (creatinine clearance 15–50 mL/min)	5 twice a day 2.5 twice a day
Half-life (h)	40	12–17	5–12	12–15
Peak effect	4–5 d	1–6 h	2–4 h	3–4 h
Renal clearance (%)	None	80	36	27
Excluded creatinine clearance in trial (mL/min)	—	<30	<30	<25
Dialyzable	No	Yes	No	No
Reversal agent	Vitamin K	None	None	None

[a] RE-LY trial.[78]
[b] ROCKET AF trial.[80]
[c] ARISTOTLE trial.[79]

AF or for chronic around-the-clock therapy. A β-blocker or a nondihydropyridine calcium channel blocker should be given at least 30 minutes before class IC agents to prevent rapid 1:1 atrioventricular conduction during atrial flutter.[84] By blocking sodium channels, class IC drugs inhibit cardiac repolarization and prolong the QRS duration. This effect is progressive at faster heart rates. Exercise stress testing immediately after drug initiation can be performed to ensure that QRS duration remains within normal limits.

In patients who are not candidates for class IC drugs or in whom class IC drugs were ineffective, long-term rhythm control can be pursued using class III agents, which include dofetilide, dronedarone, sotalol, and amiodarone. Two studies, SAFIRE-D (Symptomatic Atrial Fibrillation Investigative Research on Dofetilide)[85] and DIAMOND(Danish Investigation of Arrhythmia and Mortality on Dofetilide),[86] showed maintenance of sinus rhythm using dofetilide in 58% (compared with 25% with placebo) and 79% (compared with 42% with placebo) of patients at 1 year, respectively. Initiation of dofetilide requires inpatient admission for ECG monitoring, because it may prolong the QT interval. It is almost exclusively cleared by the kidneys, and renal function and corrected QT should be monitored at least every 3 months.

Dronedarone is a structural analogue of amiodarone with a more favorable side effect profile. It should not be used in patients with recently

Table 2
Outcomes for target-specific oral anticoagulants compared with warfarin in nonvalvular AF

TSOA	Major Bleeding	Myocardial Infarction	Stroke	Death
Dabigatran 110 mg[a]	0.80 (0.69–0.93) *P* = .003	1.35 (0.98–1.87) *P* = .07	0.92 (0.74–1.13) *P* = .41	0.91 (0.80–1.03) *P* = .13
Dabigatran 150 mg[a]	0.93 (0.81–1.07) *P* = .31	1.38 (1.00–1.91) *P* = .048	0.64 (0.51–0.81) *P*<.001	0.88 (0.77–1.00) *P* = .051
Rivaroxaban 20 mg[b]	1.04 (0.90–1.20) *P* = .58	0.81 (0.63–1.06) *P* = .12	0.88 (0.74–1.03) *P* = .12	0.92 (0.82–1.03) *P* = .15
Apixaban 5 mg[c]	0.68 (0.61–0.75) *P*<.001	0.88 (0.66–1.17) *P* = .37	0.79 (0.66–0.95) *P* = .01	0.89 (0.80–0.998) *P* = .047

[a] Data from RE-LY trial,[78] results reported as relative risk.
[b] Data from ROCKET AF trial,[80] results reported as hazard ratios.
[c] Data from ARISTOTLE trial,[79] results reported as hazard ratios.

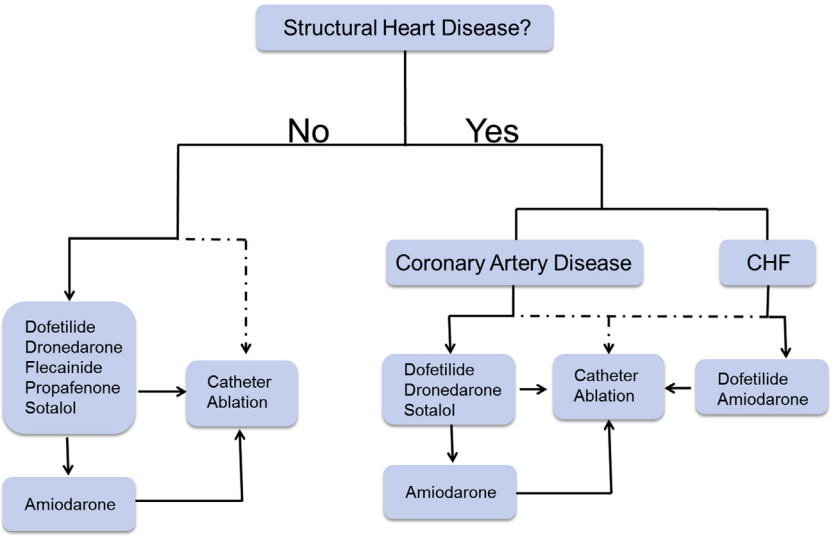

Fig. 2. Use of antiarrhythmic agents in different patient populations. Catheter ablation (*dashed line*) is recommended as a first-line therapy only in patients with paroxysmal AF. CHF, congestive heart failure. (*Data from* Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006;114:e257–354.)

decompensated heart failure with reduced ejection fraction, because of an observed increase in mortality.[87] When compared with placebo, the use of dronedarone in patients with persistent AF was associated with increased rates of heart failure, stroke, and death from cardiovascular causes. Therefore, its use has been limited to patients with paroxysmal AF.[88]

Sotalol, a β-blocker with class III properties, has been shown to have similar rates of conversion to sinus rhythm when compared with amiodarone but a lower probability of maintaining sinus rhythm.[89] In patients with ischemic heart disease, sotalol has similar efficacy for maintenance of sinus rhythm when compared with amiodarone. Sotalol should not be used in patients with decreased left ventricular ejection fraction or with left ventricular hypertrophy (wall thickness >1.5 cm). Many experts choose to initiate sotalol therapy in the inpatient setting for ECG and QT interval monitoring.

Although amiodarone can be used in more clinical scenarios compared with the other class III agents, it also carries a significant side effect profile. Adverse effects are common, with prevalence up to 15% in the first year and as high as 50% with long-term use.[90,91] **Table 4** details the HRS recommendations for routine laboratory and diagnostic testing in patients receiving amiodarone.[92]

Table 3
Antiarrhythmic agents used for rhythm control of paroxysmal and persistent AF

Drug	Structurally Normal Heart	Coronary Artery Disease	Heart Failure with Reduced Ejection Fraction	Left Ventricular Hypertrophy
Dofetilide[a]	✓	✓	✓	
Dronedarone	✓	✓		✓
Flecainide[b]	✓			
Propafenone[b]	✓			
Sotalol[a]	✓	✓		
Amiodarone	✓	✓	✓	✓

[a] Use with caution in patients at risk for torsades de pointes.
[b] Should be used with atrioventricular nodal blocking agents.

Table 4
Recommended routine monitoring for patients receiving amiodarone

Test	Timing
Liver function tests	Baseline and every 6 mo
Thyroid function tests	Baseline and every 6 mo
Electrolytes, serum creatinine	Baseline and as indicated
Chest radiograph	Baseline and annually
Pulmonary function tests, with D_{LCO} (carbon monoxide diffusion in the lung)	Baseline and for unexplained dyspnea or new chest radiographic findings
Ophthalmologic evaluation	If visual impairment or for symptoms
ECG	Baseline and annually

Radiofrequency Ablation

Radiofrequency catheter ablation (RFA) of AF has evolved as an effective treatment modality to eliminate AF over the last decade. Although antiarrhythmic drugs are often used initially to control AF, RFA can be considered as a first-line treatment in appropriately selected patients. Two randomized controlled trials have compared RFA with antiarrhythmic therapy as first-line rhythm control for patients with paroxysmal AF. In the RAAFT-2 trial,[93] patients randomized to RFA had lower rates of recurrence of AF at 1 and 2 years compared with patients randomized to antiarrhythmic therapy. In the MANTRA-PAF trial,[94] patients randomized to RFA as first-line therapy had lower AF burden at 2 years and had significant increases in physical component of the SF-36 quality of life score. Many cases of recurrent AF after RFA occur in the first 3 to 6 months and do not necessarily exclude long-term success. Several studies have evaluated long-term outcomes after RFA and have described 47% to 56% success in maintenance of sinus rhythm at 5 years after a single RFA.[95–97]

Several observational studies have suggested that RFA may help reduce the risk of stroke in patients with AF.[98,99] In a large study of patients who underwent RFA compared with age-matched and sex-matched controls with and without AF,[100] patients with AF after RFA had a significantly lower risk of stroke compared with selected patients with AF who do not undergo RFA independent of baseline stroke risk score. However, patients with AF who undergo RFA may represent a healthier population, as suggested by the small risk of mortality and stroke over a long follow-up period. Furthermore, it is possible that subsequent care after ablation may affect outcomes associated with AF. It is unclear whether the reduction in stroke observed in this and other observational studies is related to maintenance of sinus rhythm, anticoagulation, or other procedural and patient-related characteristics. Therefore, management of thromboembolic risk after RFA should be individualized, and clinical risk factors should be carefully considered regardless of whether RFA was performed.

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