JAMA | Review

Atrial Fibrillation
A Review

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IMPORTANCE In the US, approximately 10.55 million adults have atrial fibrillation (AF). AF is associated with significantly increased risk of stroke, heart failure, myocardial infarction, dementia, chronic kidney disease, and mortality.

OBSERVATIONS Symptoms of AF include palpitations, dyspnea, chest pain, presyncope, exertional intolerance, and fatigue, although approximately 10% to 40% of people with AF are asymptomatic. AF can be detected incidentally during clinical encounters, with wearable devices, or through interrogation of cardiac implanted electronic devices. In patients presenting with ischemic stroke without diagnosed AF, an implantable loop recorder (ie, subcutaneous telemetry device) can evaluate patients for intermittent AF. The 2023 American College of Cardiology (ACC)/American Heart Association (AHA)/American College of Clinical Pharmacy (ACCP)/Heart Rhythm Society (HRS) Guideline writing group proposed 4 stages of AF evolution: stage 1, at risk, defined as patients with AF-associated risk factors (eg, obesity, hypertension); stage 2, pre-AF, signs of atrial pathology on electrocardiogram or imaging without AF; stage 3, the presence of paroxysmal (recurrent AF episodes lasting ≤7 days) or persistent (continuous AF episode lasting >7 days) AF subtypes; and stage 4, permanent AF. Lifestyle and risk factor modification, including weight loss and exercise, to prevent AF onset, recurrence, and complications are recommended for all stages. In patients with estimated risk of stroke and thromboembolic events of 2% or greater per year, anticoagulation with a vitamin K antagonist or direct oral anticoagulant reduces stroke risk by 60% to 80% compared with placebo. In most patients, a direct oral anticoagulant, such as apixaban, rivaroxaban, or edoxaban, is recommended over warfarin because of lower bleeding risks. Compared with anticoagulation, aspirin is associated with poorer efficacy and is not recommended for stroke prevention. Early rhythm control with antiarrhythmic drugs or catheter ablation to restore and maintain sinus rhythm is recommended by the 2023 ACC/AHA/ACCP/HRS Guideline for some patients with AF. Catheter ablation is first-line therapy in patients with symptomatic paroxysmal AF to improve symptoms and slow progression to persistent AF. Catheter ablation is also recommended for patients with AF who have heart failure with reduced ejection fraction (HFrEF) to improve quality of life, left ventricular systolic function, and cardiovascular outcomes, such as rates of mortality and heart failure hospitalization.

CONCLUSIONS AND RELEVANCE AF is associated with increased rates of stroke, heart failure, and mortality. Lifestyle and risk factor modification are recommended to prevent AF onset, recurrence, and complications, and oral anticoagulants are recommended for those with an estimated risk of stroke or thromboembolic events of 2% or greater per year. Early rhythm control using antiarrhythmic drugs or catheter ablation is recommended in select patients with AF experiencing symptomatic paroxysmal AF or HFrEF.

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In the US, atrial fibrillation (AF) affects up to 1 in 3 people in their lifetime and was estimated to affect approximately 10.55 million (95% CI, 10.48-10.62 million) people by 2019.[1-3] Significant complications associated with AF include ischemic stroke, heart failure (HF), myocardial infarction, chronic kidney disease, dementia, and mortality. Oral anticoagulants (OACs) have reduced rates of stroke and mortality in patients with AF.[4] This review summarizes current evidence regarding the epidemiology, pathophysiology, diagnosis, and management of AF (**Box**).

Methods

We conducted a PubMed search for English-language articles published between January 1, 1990, and August 15, 2024, about the epidemiology, pathophysiology, clinical presentation, prognosis, and management of AF. Current guidelines, randomized clinical trials, and studies with larger sample sizes were prioritized for inclusion. The 107 articles comprising this review included 48 randomized clinical trials; 19 meta-analyses; 12 guidelines, consensus documents, or scientific statements; 23 longitudinal and 2 cross-sectional observational studies; and 3 reviews.

Epidemiology

The incidence, prevalence, and lifetime risk of AF are increasing,[5,6] most likely due to population aging, increased detection rates, and increased survival with AF and other cardiovascular diseases.[6,7] Spanning 50 years of Framingham Heart Study participant surveillance (1958-1967 and 1998-2007), the age-adjusted incidence per 1000 person-years increased from 3.7 to 13.4 in men and 2.5 to 8.6 in women and the prevalence increased from 20.4 to 96.2 in men and 13.7 to 49.4 in women.[7]

The incidence and prevalence of AF vary by region and demographic factors, including sex and age. The Global Burden of Disease project estimated that in 2021, 52.55 million individuals (95% CI, 43.49-63.74 million) worldwide had AF or atrial flutter, with the highest prevalence observed in high-income countries in North America, Australasia, and Western Europe.[5] The global prevalence was higher in men (~28 million) vs women (~25 million).[5] Older age is associated with higher incidence of AF (hazard ratio [HR] per 5-year increase in age, 1.66 [95% CI, 1.59-1.74]).[8]

Older age, current smoking, taller height, greater weight, higher blood pressure (systolic, diastolic, and hypertension treatment), presence of diabetes, and presence of heart disease (HF or myocardial infarction) are associated with higher rates of AF.[8-10] Risk of AF is also affected by genetic factors. Compared with individuals in the upper third of both clinical (CHARGE-AF score) and polygenic risk (48.2% [95% CI, 41.3%-55.1%]), individuals in the lower third had less than half the lifetime risk of AF (22.3% [95% CI, 15.4%-29.1%]).[2]

Additional factors associated with increased AF risk include more than moderate alcohol use (defined as >1 standard alcoholic drink per day or binge drinking), sleep apnea, and hyperthyroidism.[4,11-13] Compared with sedentary lifestyle, physical activity is associated with lower risk of AF. However, male endurance athletes have higher risk.[4,14] Although most data relating risk factors to AF are observational, Mendelian randomization studies support causal relations between multiple risk factors, including adiposity, smoking, alcohol consumption, and hypertension.[4,15]

Box. Frequently Asked Questions About Atrial Fibrillation (AF)

Among patients with AF, who should receive anticoagulation for stroke and thromboembolism prevention?

In patients with estimated risk of ischemic stroke or thromboembolic events of 2% or greater per year, benefits of anticoagulation exceed risks of major bleeding. Several risk scores identify patients at high risk of stroke, including CHA_2DS_2-VASc score, which assigns 1 point for congestive heart failure, 1 point for hypertension, 1 point for age 65 years and older, 2 points for age 75 years and older, 2 points for previous stroke or transient ischemic attack, 1 point for vascular disease, and 1 point for female sex. Anticoagulation should be continued indefinitely unless a contraindication, such as bleeding, develops.

What therapies should be recommended for patients at increased risk of AF?

Lifestyle and risk factor modification, including weight loss, moderate exercise, smoking cessation, reducing alcohol consumption, and optimal blood pressure control, are recommended to prevent AF in patients at increased risk.

How should an asymptomatic patient with new-onset AF be treated?

Patients younger than 70 years with new-onset AF may benefit from rhythm control with cardioversion and initiation of an antiarrhythmic drug, even if AF is asymptomatic. Rhythm control should also be considered for patients with heart failure or left ventricular systolic dysfunction. Anticoagulation should be initiated if the stroke or thromboembolic event risk score is 2% or greater per year.

Pathophysiology

Ectopic atrial premature beats that initiate AF typically arise from myocardial cells (sleeves) that extend a few centimeters from the pulmonary vein–atrial junction into the pulmonary veins. Although atrial ectopy may initiate AF, persistence of AF is often due to disease-specific atrial electrophysiologic, structural, and histopathologic changes that promote electrical reentry and AF continuance.[16] For example, hypertension activates the renin-angiotensin-aldosterone system, which induces atrial fibrosis and hypertrophy, slowing atrial conduction and promoting reentry and AF.[17] Obesity increases oxidative stress, systemic inflammation, and abnormal Ca^{2+}cycling. These effects increase atrial ectopy and pathologic changes that sustain arrhythmic activity. Autonomic dysfunction (eg, with sleep-disordered breathing) alters atrial repolarization and promotes AF.[17] AF-associated diseases, such as hypertension, obesity, and valvular heart disease (eg, mitral valve stenosis, mitral valve regurgitation), are associated with atrial pathology and AF.[18]

AF Screening and Detection

The probability of AF detection increases with electrocardiogram (ECG) monitoring duration. The benefits of screening for AF in the general population to detect asymptomatic AF are currently uncertain.[4] An implantable loop recorder (ILR) is a subcutaneous device that can continuously monitor heart rhythm for about 4 years. The LOOP Study (Implantable Loop Recorder Detection of Atrial Fibrillation to Prevent Stroke) randomized 6004 patients aged 70 to 90 years with 1 or more of 4 comorbidities (hypertension, diabetes, prior stroke, or HF) to ILR or usual care.[19] During

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a median of 64.5 months of follow-up, AF was diagnosed in 31.8% of the ILR group vs 12.2% of the control group. Even though OACs were initiated in patients diagnosed with incident AF, there was no significant difference (HR, 0.80 [95% CI, 0.61-1.05]) in risk of the primary outcome of stroke or systemic arterial embolism in patients randomized to ILR (0.88 events per 100 person-years [95% CI, 0.68-1.12] vs the control group, 1.09 events [95% CI, 0.96-1.24]).

Many individuals use wearable devices that evaluate heart rhythm for AF. In the Apple Heart Study, only 34% of those who received the smartwatch's notification for AF were subsequently diagnosed with AF using ECG patch monitoring.[20] AF detected by consumer wearable devices (eg, smartwatches) should be confirmed with ECG correlation or through additional testing (eg, with an ECG patch monitor).

In patients with ischemic stroke or systemic thromboembolism without established AF, ILR is a reasonable diagnostic measure to increase probability of AF detection if maximum sensitivity is sought[4] to identify patients who may benefit from OACs for secondary stroke prevention. For secondary stroke prevention, OACs are contraindicated in patients without AF or in those without a known cardioembolic source.[21,22] In randomized clinical trials of patients with ischemic stroke, rates of AF detection were 12% to 15%[23-25] after 1 year and 30%[23] by 3 years with ILR, compared with rates of 1.8% to 4.7% after 1 year and 3% after 3 years in those who received usual care or wore a 30-day monitor.

AF diagnosed during hospitalization for noncardiac illnesses, such as sepsis or noncardiac surgery, is associated with posthospital AF recurrence, stroke, and mortality.[4,26,27] In patients with severe sepsis, new-onset AF was associated with 2.7-fold (2.6% vs 0.6%) increased risk of in-hospital ischemic stroke and 7% (56% vs 39%) higher risk of in-hospital death, adjusting for demographics, comorbidities, and sepsis-associated factors.[27] Patients diagnosed with AF during hospitalization for noncardiac illness have 5-year recurrence rates of 42% to 68%.[28,29] The 2023 American College of Cardiology (ACC)/American Heart Association (AHA)/American College of Clinical Pharmacy (ACCP)/Heart Rhythm Society (HRS) Guideline recommends that patients diagnosed with AF during hospitalization for noncardiac illness be counseled about their increased risk of recurrent AF.[4] Whether long-term OACs should be initiated at the time of hospital discharge or deferred until AF recurs during subsequent follow-up remains unclear.[30]

In patients without diagnosed AF who have cardiac implanted electronic devices, including an ILR, pacemaker, or implantable cardioverter-defibrillator, the incidence of atrial high-rate episodes (AHREs; defined as asymptomatic atrial tachyarrhythmias with atrial rates >190 beats per minute, which include AF, atrial flutter, and atrial tachycardias) detected is approximately 24.5% to 34.4% over 1 to 2.5 years of follow-up.[31,32] Such patients may or may not have underlying cardiomyopathy or conduction disease. Although the duration threshold for meaningful AHREs has varied among studies, from longer than 20 seconds to 24 hours, AHREs of greater than 6 minutes are associated with incident AF.[31] A meta-analysis of 15 353 participants reported that AHREs were associated with 2.4-fold increased risk of stroke (1.89 per 100 person-years with vs 0.93 per 100 person-years without) that increased with AHRE duration.[33] A meta-analysis of 2 randomized clinical trials that included 6548 patients studied whether OACs (vs no anticoagulation or low-dose aspirin) were associated with lower rates of stroke in those with AHRE lasting 6 minutes or longer. In this meta-analysis, direct OACs (DOACs) were associated with lower relative risk (RR) of stroke by 32% (2.0% vs 3.0%), but were associated with 39% increased RR of major bleeding (4.8% vs 3.2%).[34] The ischemic stroke rate was 1% per patient-year in the control group (patients with AHREs not on DOACs), a significant stroke risk with AHREs, but lower than the literature-estimated 2% per patient-year for patients with diagnosed AF (detected on 12-lead ECG). It is reasonable to initiate OACs for AHREs lasting longer than 24 hours in individuals with CHA_2DS_2-VASc scores of 2 or higher. It may be reasonable for AHREs lasting longer than 5 minutes in those with CHA_2DS_2-VASc score of 3 or higher, but bleeding risk should be carefully considered.[4]

Clinical Presentation

Typical symptoms of AF include palpitations with or without dyspnea, chest pain, presyncope, exertional intolerance, and fatigue. Approximately 10% to 40% of people with AF are asymptomatic.[4] Asymptomatic AF may be detected during routine clinical encounters or with a wearable monitor or cardiac implanted electronic device interrogation. Asymptomatic initial presentation of AF is more common in men (10% in men vs 3% in women) and older adults (mean age, 74 years vs 62 years for symptomatic people).[35,36] Diabetes is more common in those with asymptomatic AF. Asymptomatic AF may also be discovered during evaluation of AF-related clinical outcomes, such as ischemic stroke, systemic thromboembolism, myocardial infarction, or HF.

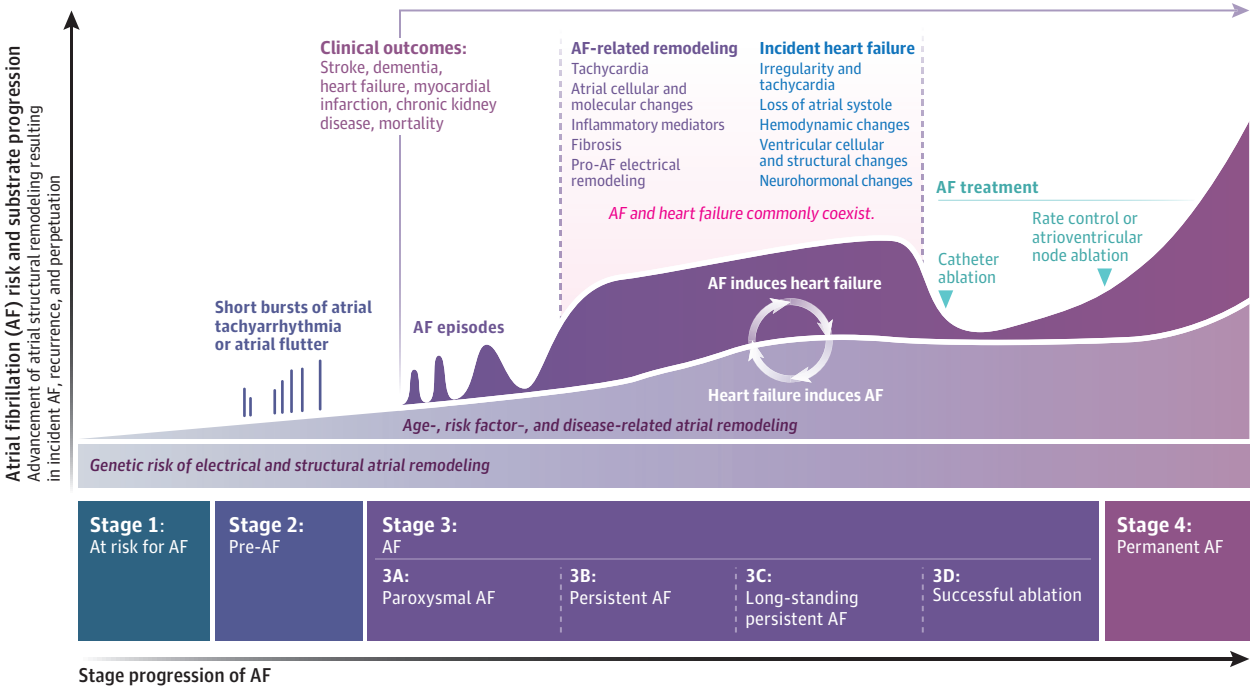
AF and HF are predisposing conditions for each other and often coexist at the time of incident AF (**Figure 1**).[37] In patients with AF and newly diagnosed HF and reduced ejection fraction (HFrEF), tachycardia-mediated cardiomyopathy should be considered when common etiologies (eg, ischemia) have been excluded.[4]

The diagnosis of AF is confirmed by identifying irregular atrial activity (fibrillatory waves) without discrete P waves on 12-lead ECG[4] or lasting for longer than 30 seconds on rhythm strip. AF is classified as paroxysmal (intermittent AF episodes lasting ≤7 days), persistent (continuous AF episodes lasting >7 days and/or requiring cardioversion), or long-standing persistent (AF episode lasting >1 year). AF subtype is determined by initial clinical presentation and may reflect severity of atrial pathology.[18] In some cases, the AF subtype may not be apparent at time of diagnosis; its persistence or spontaneous termination during the subsequent week allow for classification.

Evaluation of patients with newly identified AF should include transthoracic echocardiogram to assess cardiac structure and to identify possible causes for AF (eg, valve disease)[4] or outcomes associated with AF (eg, reduced ventricular function). Basic laboratory testing, including complete blood count, metabolic panel, and thyroid function, is appropriate.[4] Additional testing, such as cardiac stress testing in patients with newly diagnosed AF, should not be routinely performed without specific indications, such as angina or reduced ejection fraction.[4] Outpatient evaluation and management is appropriate for patients with asymptomatic or mildly symptomatic AF in the absence of HF, ischemia, or poorly controlled ventricular rates.

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Figure 1. Atrial Fibrillation Stages and the Evolution of Atrial Pathology



AF stages are reflective of the evolution of AF and include those at risk (stage 1), those with pre-AF (stage 2), those with AF (stage 3), and those with permanent AF (stage 4). Genetic-, age-, risk factor–, and disease-related remodeling generate the AF substrate, defined as any combination of molecular, cellular, structural, or electrical changes to the atrium that increase susceptibility for and perpetuation of AF. As AF substrate advances, AF may become more persistent. Heart failure and AF commonly coexist, and this figure highlights the feedforward interaction and effect of treatment on clinical outcomes.

Emergency department referral may be indicated for hemodynamically unstable or highly symptomatic AF, AF with concomitant HF, or AF with rapid ventricular rates. Emergent cardioversion should be considered for hemodynamic instability attributable to AF.[4] The risk of thromboembolism must be carefully considered, particularly if a patient has not been on therapeutic anticoagulation or if the AF duration has persisted for longer than 48 hours and imaging with transesophageal echocardiogram or cardiac computed tomography to exclude left atrial thrombus is not immediately feasible.

Classification Scheme: Stages of AF

AF is no longer categorized according to valvular or nonvalvular AF.[4] This distinction is only currently used to guide OAC strategy.

Four AF stages have been proposed (Figure 1).[4] Individuals with modifiable and nonmodifiable risk factors, such as obesity or family history of AF, are classified as stage 1 at risk for AF. Stage 2, pre-AF, is defined as the presence of atrial pathology, including left atrial enlargement, frequent atrial ectopy, or nonsustained atrial tachycardia, but without diagnosed AF. Individuals with conditions associated with high incidence of AF, such as atrial flutter, HF, coronary artery disease, valvular heart disease, hypertrophic cardiomyopathy, neuromuscular diseases, and hyperthyroidism, are considered to have pre-AF; clinicians may consider increased AF surveillance consisting of a wearable or implantable monitor. However, no randomized clinical trials have demonstrated that surveillance for AF prevents adverse outcomes. Stage 3 AF is clinically apparent AF and is categorized as 1 of 4 subtypes: 3a, paroxysmal (recurrent AF episodes lasting ≤7 days); 3C, persistent AF (continuous AF episode lasting >7 days); 3C, long-standing persistent AF (continuous AF episode lasting >1 year); or a new subtype, 3d, in which AF was treated successfully with catheter ablation. After catheter ablation, AF episodes may be less symptomatic, less frequent, or shorter in duration.[4] Individuals with stage 4 AF have permanent AF, for which a decision has been made not to pursue rhythm control based on patient and clinical factors, such as age and AF duration.

Prognosis

In a meta-analysis of 9 686 513 patients, compared with absence of diagnosed AF, AF was associated with absolute risk increase per 1000 participant-years of approximately 3.6 for stroke, 11.1 for HF, 1.4 for ischemic heart disease, 6.6 for chronic kidney disease, and 3.8 for mortality (**Table 1** includes RRs).[38] A meta-analysis reported AF was associated with increased risk of Alzheimer disease (adjusted OR [aOR], 1.4) and vascular dementia (aOR, 1.7), and in stroke-free patients (n = 324 494), cognitive impairment or dementia (adjusted HR [aHR], 1.4; absolute numbers unavailable).[40] In randomized clinical trials evaluating DOACs vs warfarin, patients who received apixaban (HR, 0.79) had an annual stroke or systemic embolism rate of 1.3% compared with 1.6% for warfarin.[41-44]

In a community-based cohort of 3491 adults with AF, incidence rates per 100 person-years of follow-up were 2.13 (95% CI, 1.88-2.40) for HFrEF and 3.32 (95% CI, 3.01-3.66) for HF with preserved ejection fraction (HFpEF).[45] Although AF is associated with increased rates of HF (Table 1), randomized clinical trials have not established treatments among people with AF that prevent HF.[6,38,39]

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Table 1. Relative, 5-Year, and Lifetime Risks and Restricted Mean Time Lost With Various Atrial Fibrillation (AF) Outcomes

	Odutayo et al[38]		Piccini et al[39]	Vinter et al[6]	
Study design	Systematic review and meta-analysis		Fee-for-service Medicare beneficiaries aged ≥65 y; incident AF, 1999-2007	Danish population-based study, 3.5 million individuals free of AF at index age 45 y, 2000-2022	
Outcome	Relative risk (95% CI)	Absolute rate per 1000 participant-y[a]	5-y risk, %	Lifetime risk, % (95% CI)[b]	Restricted mean time lost, y[c]
Stroke	2.42 (2.17-2.71)	3.6	7.1	21.4 (20.6-22.3)	6.2 (5.9-6.6)
Heart failure	4.99 (3.04-8.22)	11.1	13.7	41.2 (39.8-42.7)	13.6 (12.9-14.3)
Myocardial infarction	1.61 (1.38-1.87)[d]	1.4[d]	3.9	11.5 (10.9-12.2)	3.6 (3.3-3.9)
All-cause mortality	1.46 (1.39-1.53)	3.8	48.8		

[a] Absolute rate data are unavailable for Piccini et al[39] and Vinter et al.[6]

[b] Lifetime risk is the cumulative incidence function at age 95 years.

[c] Restricted mean time lost is the number of disease-free years lost by age 95 years.

[d] Odutayo et al meta-analyzed ischemic heart disease instead of myocardial infarction.

In a study of 9769 patients with AF who were taking 1 of 4 OACs (apixaban, dabigatran, rivaroxaban, or warfarin), use of DOACs was associated with lower rates of acute kidney injury (HR, 0.68 [95% CI, 0.58-0.81]).[9]

Treatments

Recommended treatment of patients at risk for AF (stages 1 or 2) or with AF (stages 3 or 4) consists of lifestyle and risk factor modification, such as weight loss, exercise, and targeted blood pressure control. However, except for hypertension treatment, randomized clinical trial evidence that these lifestyle and risk factors prevent AF does not exist. Lifestyle and risk factor modification is also recommended for patients with AF who are treated with antiarrhythmic drugs (AADs) or ablation (**Figure 2**).[4]

Primary Prevention: Risk Factors

The 2023 ACC/AHA/ACCP/HRS Guideline recommends lifestyle and risk factor modification for individuals with stages 1 and 2 AF, including treating obesity, diabetes, cigarette smoking, and hypertension, and recommendations to address physical inactivity and unhealthy alcohol consumption.[4] In secondary analysis of randomized clinical trial data, intensive blood pressure control (ie, lowering systolic blood pressure to <120 mm Hg, compared with <140 mm Hg) was associated with lower AF risk (6.21 vs 8.33 events per 1000 person-years; HR, 0.74 [95% CI, 0.56-0.98]).[46] A meta-analysis of 20 randomized clinical trials that included 63 604 patients with diabetes, HF, or kidney disease reported that sodium-glucose cotransporter-2 inhibitors were associated with reduced AF risk (RR, 0.82 [95% CI, 0.72-0.93]; absolute numbers unavailable).[47]

Secondary Prevention

Although treatment of lifestyle and risk factors has been recommended for many years, these preventive strategies are not widely implemented.[48-51] The 2023 ACC/AHA/ACCP/HRS Guideline emphasized class 1 recommendations for weight loss, exercise, smoking cessation, minimization or elimination of alcohol consumption, optimal blood pressure control, and a comprehensive care program (**Table 2**) for improvement in outcomes,[4,52-56] which is similar to the recently published European AF guidelines.[51]

Stroke and Cognitive Disease Prevention

In patients with estimated risk of ischemic stroke or thromboembolic events 2% or greater per year (eg, CHA_2DS_2-VASc ≥2 for men, ≥3 for women), benefits of OACs exceed risks of major bleeding.[4] OAC therapy is associated with reduced rates of cognitive impairment and dementia.[57] Several risk scores identify patients at high risk of stroke, with the CHA_2DS_2-VASc score being the most widely validated, which assigns 1 point for congestive HF, 1 point for hypertension, 1 point for age 65 years and older, 2 points for age 75 years and older, 2 points for previous stroke or transient ischemic attack, 1 point for vascular disease, and 1 point for female sex.[4]

In patients without mechanical heart valves or moderate to severe mitral stenosis, DOACs are preferred because they are associated with less bleeding than warfarin. All DOACs reduce risk of intracranial hemorrhage by approximately half compared with warfarin.[41-44,58] After ablation, OACs should be continued for at least 3 months; subsequent decisions should be guided by patients' stroke risk.[4] Ongoing clinical studies are evaluating the safety of discontinuing OACs in patients who have undergone ablation and have no apparent recurrence of AF.[4]

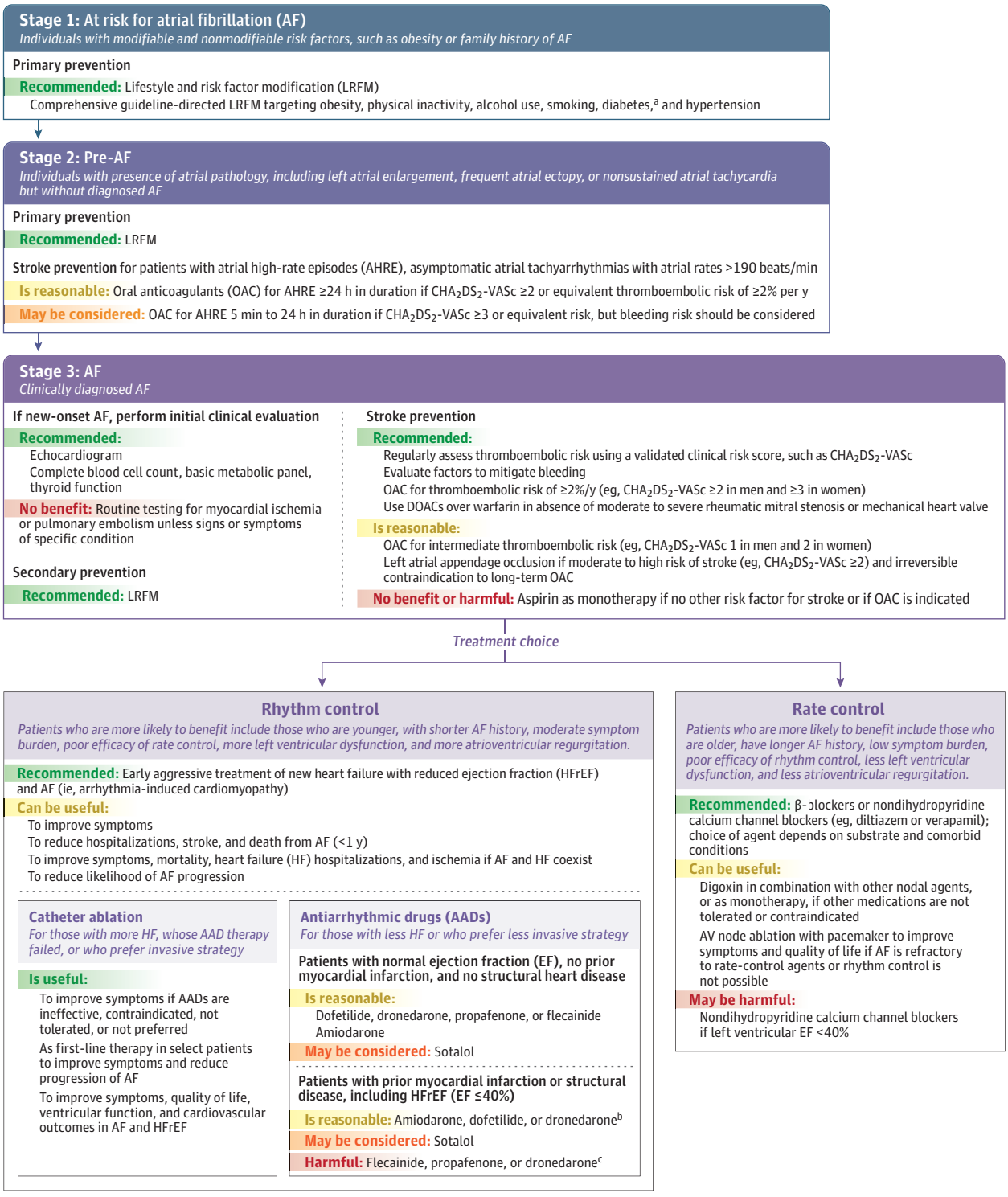
No definitive randomized clinical trials have directly compared the efficacy and safety of 1 DOAC with another.[4] The American Geriatrics Society recommends that because of higher bleeding rates compared with other DOACs, rivaroxaban should be avoided in adults 65 years and older with AF, except when once-daily dosing may improve medication adherence.[59] Apixaban and rivaroxaban are approved for patients receiving dialysis based on limited pharmacokinetic data.[4]

In patients with AF eligible for OACs who do not have a clinical condition requiring treatment with antiplatelet drugs, aspirin alone or aspirin plus clopidogrel as an alternative to OACs are considered harmful because they are less effective than OACs for preventing cardioembolic stroke in AF despite similar bleeding risk.[4,51] Compared with placebo, aspirin does not lower risk of stroke, but is associated with increased major bleeding risk.[4,60] Adding antiplatelet drugs to OACs increases risk of bleeding and is recommended only after acute coronary syndrome or percutaneous coronary intervention (PCI). Based on randomized clinical trials evaluating post-PCI antithrombotic regimens,[61-64]

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Figure 2. Treatment Care Pathway



Treatment care pathway adapted from 2023 ACC/AHA/ACCP/HRS guideline.[4] Color codes represent class of recommendation. Green indicates class 1 benefit>>>risk; yellow, class 2a benefit>>risk; orange, class 2b benefit≥risk; and red, class 3, no benefit or harm. This figure has not been validated for clinical use.

[a]Diabetes management did not receive a class 1 recommendation for secondary prevention in the US AF guideline,[4] but did in the European AF guideline.[51]

[b]Without recent decompensated HF or severe left ventricular dysfunction.

[c]With New York Heart Association class III or IV HF or HF decompensation in past 4 weeks.

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Table 2. Benefits of Adhering to ACC/AHA/ACCP/HRS Guideline Regarding Lifestyle and Risk Factor Modification for Secondary Prevention of Atrial Fibrillation (AF)

			Associated benefits of adhering to recommendations[c]							
Risk factor	Level of evidence[a]	Recommendation[b]	AF symptoms	AF burden[d]	Maintenance sinus rhythm	AF recurrence[e]	AF progression[f]	Functional capacity	Quality of life	AF complications
Overweight or obesity	B-R[4,52]	Weight loss, targeting ≥10% weight reduction	Decreased	Decreased	Increased	Decreased	Decreased			
Physical fitness[g]	B-R[4,53]	Moderate to vigorous exercise training, targeting 210 min per week	Decreased	Decreased	Increased	Decreased		Increased	Improved	Decreased
Cigarette smoking	B-NR[4,54]	Advised to quit smoking and receive goal-directed medical therapy for tobacco cessation								Decreased
Alcohol consumption	B-R[4,55]	Individuals seeking rhythm control should minimize or eliminate alcohol consumption	Decreased	Decreased		Decreased	Decreased			
Hypertension	B-NR[4,56]	Optimal blood pressure control				Decreased				Decreased
Comprehensive care	A[4]	Comprehensive care addressing lifestyle and risk factor modification, AF symptoms, risk of stroke, and other associated medical conditions		Decreased			Decreased			Decreased

Abbreviations: ACC, American College of Cardiology; ACCP, American College of Clinical Pharmacy; AHA, American Heart Association; HRS, Heart Rhythm Society; RCT, randomized clinical trial.

[a] Level of evidence A is high quality from >1 RCT, meta-analysis of high-quality RCTs, or ≥1 RCT corroborated by high-quality registries; B-R, moderate quality from ≥1 RCT or meta-analysis of moderate-quality RCTs; B-NR, moderate-quality evidence from ≥1 well-designed, well-executed nonrandomized study, observational study, or registry study, or meta-analysis of such studies.

[b] Class of recommendation 1 represents the strongest recommendation, as benefit outweighs risk. All recommendations included in the Table are Class 1.

[c] Blank cells indicate that no data were available.

[d] AF burden has several meanings (study dependent), including AF symptom severity and percentage of time spent in AF (duration and number of episodes).

[e] AF recurrence includes studies postablation.

[f] AF progression indicates progression in AF stage (eg, paroxysmal to persistent AF or persistent to permanent).

[g] Exercise training is recommended in patients without AF in the setting of excessive exercise training.

DOACs should be recommended instead of warfarin for patients with AF undergoing PCI.[4] Aspirin should be discontinued early (1-4 weeks) after PCI with continuation of OAC plus P2Y12 inhibitor (clopidogrel preferred over ticagrelor or prasugrel)[65] over triple antithrombotic therapy (OAC, aspirin, and P2Y12 inhibitor) to reduce clinically relevant bleeding risk.[4]

Current guidelines recommend OAC monotherapy over OAC plus single antiplatelet therapy in patients with AF and chronic coronary artery disease who have undergone coronary revascularization more than 1 year previously, unless the patient has a history of prior stent thrombosis.[4] In the Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease (AFIRE) trial, which included 2236 patients with AF, rivaroxaban monotherapy was superior to rivaroxaban plus aspirin or P2Y12 inhibitors for preventing major bleeding (HR, 0.59 [95% CI, 0.39-0.89]; $P = .01$) and noninferior for major cardiovascular events (4.14% and 5.75% per patient-year; HR, 0.72 [95% CI, 0.55-0.95]; $P < .001$).[66]

Although bleeding risk scores, such as HAS-BLED[67] and HEMORR$_2$HAGES,[68] may help inform decision-making regarding initiating OACs in patients with AF and increased risk of bleeding, these scores have limitations because they incorporate factors that are also associated with higher stroke risk. Bleeding risk scores may help identify modifiable risk factors for bleeding and the need for more frequent follow-up.[4,51]

For patients with recurrent bleeding requiring blood transfusions or who have spontaneous intracerebral hemorrhage, OACs may be contraindicated. In these patients, percutaneous left atrial appendage occlusion (pLAAO) with a self-expanding, umbrella-like device is a reasonable alternative to prevent stroke.[4] No direct evidence from randomized clinical trials exists on benefits of pLAAO in OAC-ineligible patients. pLAAO was US Food and Drug Administration–approved based on randomized clinical trials comparing pLAAO with warfarin in warfarin-eligible patients.[69-72] In patients for whom long-term OACs are contraindicated, pLAAO is reasonable with the understanding that it requires at least 45 days of OACs followed by dual antiplatelet therapy for 6 months and lifelong aspirin (325 mg).[4,69-72] Some situations, such as peri-device leak greater than 5 mm or device thrombosis, require prolonged OACs after pLAAO.[69-72]

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Table 3. Randomized Clinical Trials of Catheter Ablation for Atrial Fibrillation (AF)[a]

Source	Enrollment period	Participants, No.	Inclusion criteria	Control	Primary outcome	Length of follow-up, mo
RAAFT-1,[86] 2005	Dec 2001-Jul 2002	Ablation: 33 Control: 37	Symptomatic, untreated paroxysmal AF	AAD	Recurrence of AF >15 s Ablation: 4 (13%) AAD: 22 (63%) (*P* < .001)	12
Oral et al,[87] 2006	Nov 2002-Feb 2004	Ablation + AAD: 77 Control: 69	Persistent AF >6 mo with recurrence within 1 wk of direct current cardioversion	AAD	Freedom from AF/atrial flutter Ablation: 57 (74%) AAD: 40 (58%) (*P* = .05)	12
A4 study,[79] 2008	NA	Ablation: 53 Control: 59	Symptomatic, paroxysmal AF resistant to ≥1 AAD	AAD	Recurrent AF ≥3 min Ablation: 13 (23%) AAD: 46 (89%) (*P* < .001)	12
PABA-CHF,[88] 2008	Nov 2002-Jun 2006	Ablation: 41 Control: 40	Symptomatic paroxysmal or persistent AF resistant to ≥1 AAD, NYHA II or III HF, and LVEF ≤40%	Atrioventricular junction ablation with biventricular pacing	Composite of LVEF, 6MWT, and MLHFQ score Ablation: LVEF 35 ± 9% 6MWT 340 ± 49 m MLHFQ 60 ± 8 Control: 28 ± 6% 6MWT 297 ± 36 m, MLHFQ 82 ± 14 (*P* < .001)	6
ThermoCool AF,[89] 2010	Oct 2004-Oct 2007	Ablation: 106 Control: 61	Symptomatic, paroxysmal AF resistant to ≥1 AAD	AAD	Freedom from protocol-defined treatment failure Ablation: 66% AAD: 16% (HR, 0.30 [95% CI, 0.19-0.47]; *P* < .001)	9
MANTRA-PAF,[90] 2012	Jun 2005-Mar 2009	Ablation: 146 Control: 148	Symptomatic, untreated paroxysmal AF	AAD	Burden of AF (90th percentile) Ablation: 9% AAD: 18% (*P* = .007)	24
STOP AF,[91] 2013	NA	Ablation: 163 Control: 82	Symptomatic, paroxysmal AF resistant to ≥1 AAD	AAD	Freedom from chronic treatment failure Ablation: 114 (69.9%) AAD: 6 (7.3%) (*P* < .001)	12
RAAFT-2,[92] 2014	Jul 2006-Jan 2010	Ablation: 66 Control: 61	Symptomatic, untreated paroxysmal AF	AAD	Time to recurrence of AT >30 s Ablation: 36 (54.5%) AAD: 44 (72.1%) (HR, 0.56 [95% CI, 0.35-0.90]; *P* = .02)	24
AATAC,[93] 2016	NA	Ablation: 102 Control: 101	Persistent AF, NYHA II or III HF, LVEF ≤40%, dual chamber implantable cardioverter defibrillator/cardiac resynchronization therapy with defibrillator	AAD	Freedom from AT >30 s Ablation: 71 (70%) AAD: 34 (34%) (*P* < .001)	24
CASTLE-AF,[94] 2018	Jan 2008-Jan 2016	Ablation: 179 Control: 184	Paroxysmal or persistent AF, resistant to AAD, NYHA ≥II HF, and LVEF ≤35%	AAD or rate control	Composite of death from any cause or HF hospitalization Ablation: 51 (28.5%) AAD/rate control: 82 (44.6%) (HR, 0.62 [95% CI, 0.43-0.87]; *P* = .007)	Median, 37.8
CABANA,[83] 2019	Nov 2009-Apr 2016	Ablation: 1108 Control: 1096	Aged ≥65 y or <65 y with ≥1 stroke risk factor with paroxysmal or persistent AF	AAD or rate control	Death, disabling stroke, serious bleeding, or cardiac arrest Ablation: 89 (8%) Control: 101 (9.2%) (HR, 0.86 [95% CI, 0.65-1.15]; *P* = .30)	Median, 48.5

(continued)

Rate and Rhythm Control

The 2 primary strategies for management of AF are rate control, in which the ventricular rate is slowed with drugs that prolong the AV nodal refractory period, and rhythm control, in which therapeutic interventions aim to restore or maintain sinus rhythm. The choice of rate or rhythm control does not affect the decision for

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Table 3. Randomized Clinical Trials of Catheter Ablation for Atrial Fibrillation (AF)[a] (continued)

Source	Enrollment period	Participants, No.	Inclusion criteria	Control	Primary outcome	Length of follow-up, mo
EAST-AFNET 4,[76] 2020	Jul 2011-Dec 2016	Ablation or AAD: 1395 Control: 1394	AF for ≤12 mo	Rate control	Composite of cardiovascular death, stroke, or hospitalization for HF or acute coronary syndrome; number of nights spent in the hospital per year Rhythm control: 3.9/100 person-years Rate control: 5.0/100 person-years (HR, 0.79 [95% CI, 0.66-0.94]; *P* = .005)	24
EARLY-AF,[80] 2021	Jan 2017-Dec 2018	Ablation: 154 Control: 149	Symptomatic, untreated paroxysmal AF	AAD	Recurrence of AT >30 s Ablation: 66 (42.9%) AAD: 101 (67.8%) (HR, 0.48 [95% CI, 0.35-0.66]; *P* < .001)	12

Abbreviations: 6MWT, 6-Minute Walk Test; AAD, antiarrhythmic drug; AT, atrial tachyarrhythmia (includes atrial fibrillation, atrial flutter, or atrial tachycardia); HF, heart failure; HR, hazard ratio; LVEF, left ventricular ejection fraction; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NA, not available; NYHA, New York Heart Association.

Trial abbreviations: CABANA, Catheter Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation; CAMTAF, Catheter Ablation Versus Medical Treatment of Atrial Fibrillation in Heart Failure; CASTLE-AF, Catheter Ablation Versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction and Atrial Fibrillation; EARLY-AF, Early Aggressive Invasive Intervention for Atrial Fibrillation; EAST-AFNET 4, Early Treatment of Atrial Fibrillation for Stroke Prevention Trial; MANTRA-PAF, Radiofrequency Ablation as Initial Therapy in Paroxysmal Atrial Fibrillation; PABA-CHF, Pulmonary Vein Antrum Isolation vs AV Node Ablation with Biventricular Pacing for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure; RAAFT, Radiofrequency Ablation vs Antiarrhythmic Drugs as First-Line Treatment of Symptomatic Atrial Fibrillation; ThermoCool AF, Comparison of Antiarrhythmic Drug Therapy and Radiofrequency Catheter Ablation in Patients With Paroxysmal Atrial Fibrillation.

[a] Randomized clinical trials were selected based on citation frequency and their impact on shaping clinical guidelines.

or duration of OAC. Rhythm control interventions consist of AADs, cardioversion, and/or ablation. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and Rate Control vs Electrical Cardioversion for Atrial Fibrillation (RACE) studies compared AF strategies and showed no significant differences in clinical outcomes, including mortality and stroke.[73,74]

More recent studies reported the benefits of initiating rhythm control within 1 year of AF diagnosis (early rhythm control) over rate control for reducing HF, stroke risk, and mortality in patients with paroxysmal and persistent AF.[75-77] The benefit of early rhythm control was also observed in those with asymptomatic AF.

Rate control without attempts to treat rhythm is an appropriate strategy for patients who are unlikely to benefit from rhythm control with AADs or catheter ablation and for those in whom rhythm control is considered too risky. For example, patients with amyloid cardiomyopathy or cor pulmonale are more likely to have recurrent AF following ablation, therefore rate control may be more appropriate. Rate control is also appropriate for patients with stage 4 (permanent) AF. Rate control is achieved with single or drug combinations, including β-blockers such as metoprolol, esmolol, or atenolol, and nondihydropyridine calcium channel blockers, such as verapamil or diltiazem, to slow electrical conduction through the atrioventricular node.[4] Digoxin can be used as adjunctive therapy when ventricular rate remains poorly controlled or hypotension limits further titration of β-blockers or nondihydropyridine calcium channel blockers.[4] Drugs that slow atrioventricular conduction should be titrated to control symptoms and achieve resting heart rates less than 100 to 110 beats per minute.[4] Atrioventricular nodal ablation with pacemaker implant can be useful for controlling symptoms and improving quality of life (QOL) in patients with ineffectively controlled ventricular rates who have not improved or are not candidates for rhythm control.[4]

Pharmacologic Rhythm Control

AADs may be used for acute conversion of AF to sinus rhythm ("pill-in-the-pocket") or for suppression of AF when taken daily. Pill-in-the-pocket treatment with flecainide or propafenone in conjunction with concomitant AV nodal agent(s) may be useful for intermittent treatment of infrequent AF episodes, but efficacy for acute conversion and safety (proarrhythmic effect) must first be tested in a monitored hospital setting.[51] Patients should be observed for at least 8 hours after dose.[4]

Early rate vs rhythm randomized clinical trials did not demonstrate improved mortality or stroke risk with daily use of AAD compared with treatment with AV nodal agents.[78] However, the 2020 Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4) reported clinical benefit of rhythm control with daily AAD or catheter ablation over rate control therapy when rhythm control was initiated early (ie, within 12 months of AF diagnosis).[76] EAST-AFNET 4 randomized 2789 patients within 1 year of AF onset (median time, 36 days) and mean CHA_2DS_2-VASc of 3.4 to rhythm control or rate control. Most patients (87%) were initially treated with AADs, including flecainide (35.9%), amiodarone (19.6%), and dronedarone (16.7%), whereas 19.4% underwent ablation by 2 years. The trial was stopped early due to a 21% reduction in the primary composite outcome of cardiovascular mortality, stroke, and hospitalizations for HF or acute coronary syndrome with rhythm control vs rate control (3.9 per 100

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person-years vs 5.0 per 100 person-years).[76] The EAST-AFNET 4 trial reported that benefit of rhythm control extended to those with asymptomatic AF.[77] AADs are not atrial cardiomyocyte selective and can alter ventricular myocardial electrophysiologic properties; therefore, the presence of comorbidities, such as prior myocardial infarction or HFrEF (40%), influences AAD selection (Figure 2).

Catheter Ablation

The discovery that focal ectopic impulses arising from the pulmonary veins often initiate AF and that ablation of these sources significantly reduced AF preceded development of catheter ablation procedures, which are effective for maintaining sinus rhythm (Table 1). Ablation destroys atrial tissue at the atrial–pulmonary vein junction to prevent ectopic impulses from the pulmonary vein from reaching the atrium (ie, pulmonary vein isolation). The A4 study randomized 112 patients with paroxysmal AF to treatment with AAD or radiofrequency ablation.[79] The primary end point was longer than 3 minutes of AF or reported AF symptoms. At 1-year follow-up, 89% of patients who underwent ablation remained AF-free vs 23% of patients treated with AAD ($P < .0001$). A significant improvement in symptoms, QOL, and exercise capacity was also observed with ablation.[79]

The Early Aggressive Invasive Intervention for Atrial Fibrillation (EARLY-AF) trial randomized 303 patients with symptomatic, untreated paroxysmal AF to cryoablation or AAD and monitored for recurrent AF using ILR.[80] The primary end point was first recurrence of AF (or atrial tachyarrhythmia) of 30 seconds or longer; the secondary end point was overall burden of AF. The decision for OAC was based on risk of stroke (CHA_2DS_2-VASc ≥1) and irrespective of group assignment. At 1-year follow-up, recurrence of AF was significantly less likely in those who underwent ablation (42.9%) compared with AADs (67.8%; HR, 0.48 [95% CI, 0.35-0.66]). The mean time in AF was significantly lower with ablation (0.6%) vs AADs (3.9%). Meta-analysis of 5 clinical trials that enrolled 693 people with AF (predominately paroxysmal AF), reported a more than 2-fold greater freedom from AF at 1 year with radiofrequency ablation (77%) vs AAD (29%).[81] Ablation in patients with persistent AF (including long-standing persistent) with low prevalence of structural heart disease (eg, normal left ventricular function, normal to mild left atrial enlargement, and low prevalence of coronary artery disease or diabetes) has comparable results to those with paroxysmal AF.[82]

The Catheter Ablation Versus Antiarrhythmic Drugs for Atrial Fibrillation (CABANA) trial tested efficacy of ablation on clinical outcomes. It enrolled 2204 patients with paroxysmal or persistent AF and median CHA_2DS_2-VASc score of 3 who had previously been treated with 2 or more AADs. All patients irrespective of treatment group received anticoagulation based on stroke risk (CHA_2DS_2-VASc ≥2). CABANA reported that ablation did not significantly reduce the primary composite end point of death, disabling stroke, serious bleeding, or cardiac arrest.[83] The statistical power of the study was limited by lower-than-expected event rates, high crossover rates, and loss to follow-up. Despite this, CABANA reported significant improvement in QOL with ablation.[84] In prespecified subgroup analysis of CABANA, compared with medical treatment, patients who received ablation (intention-to-treat analysis) younger than 65 years had lower mortality, whereas those 75 years or older did not.[85]

Ablation in HF

Coexistence of HF and AF is associated with increased mortality compared with those with HF or AF alone.[37] Although AADs have limited benefit in AF patients with HFrEF, multiple randomized clinical trials and meta-analyses have shown superiority of rhythm control with ablation over medical therapy (**Table 3**).[88,93-100] The Catheter Ablation Versus Standard Conventional Treatment in Patients with Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial randomized 363 patients with HF and left ventricular ejection fraction 35% or less to ablation or medical therapy.[94] After median follow-up of 38 months, ablation was associated with significant reductions in the composite end point of death or hospitalization for HF (ablation, 28.5% vs medical therapy, 44.6%; HR, 0.62 [95% CI, 0.43-0.87]). A meta-analysis of 3 trials that included 977 patients with HF and AF reported that compared with medical therapy, ablation was associated with lower mortality rates (RR, 0.61 [95% CI, 0.44-0.84]) and HF hospitalizations (RR, 0.60 [95% CI, 0.49-0.74]; absolute rates unavailable).[101]

Few randomized clinical trials have studied the effects of ablation in people with AF and HFpEF. CABANA was the only large randomized clinical trial (n = 2204) in which nearly 80% of patients with HF had an ejection fraction of 50% or greater.[102] In a prespecified subgroup analysis of patients with New York Heart Association class greater than 2, ablation was associated with 43% reduction in all-cause mortality (6.1% ablation vs 9.3% medical therapy), 44% reduction in AF recurrence (56% ablation vs 72% medical therapy), and sustained improvement of QOL out to 5 years (adjusted mean difference, 5 points).[102]

Inequities in AF Management and Outcomes

AF management and outcomes are associated with inequities by sex, race and ethnicity, and social determinants of health (SDOH), defined as nonmedical factors that influence health. Individuals with AF who are women, Black, or Hispanic; with lower income or education; inadequate or lack of insurance; or who live in rural areas or neighborhoods characterized by material deprivation are less likely to receive guideline-directed care and more likely to experience worse outcomes.[4,103] A study from Ontario, Canada, reported that 1 year after AF diagnosis, patients residing in neighborhoods with the highest compared with the lowest material deprivation were less likely to have cardiology visits (27.9% in quintile 5 vs 34% in quintile 1; aHR, 0.84), were less likely to receive guideline-based therapies, including OACs (53.9% quintile 5 vs 56.8% in quintile 1; aHR, 0.97) and ablation (0.1% in quintile 5 vs 0.3% in quintile 1; aHR, 0.45), and experienced worse outcomes, including more strokes (1.8% in quintile 5 vs 1.4% in quintile 1; aHR, 1.15) and higher mortality (17.9% in quintile 5 vs 14.1% in quintile 1; aHR, 1.16).[104]

The US Centers for Medicare & Medicaid Services and the Joint Commission have instituted SDOH reporting requirements with the goal of reducing health inequities.[105,106]

Limitations

This review has limitations. First, relevant studies may not have been included. Second, generalizability of the evidence is limited because many clinical trials have not included substantial proportions of participants who were Black or Hispanic, and have not examined variation by SDOH.[107] Third, the quality of included evidence was not systematically reviewed.

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Conclusions

AF is associated with increased rates of stroke, heart failure, and mortality. Guideline-directed AF management includes lifestyle and risk factor modification to prevent AF onset, recurrence, and complications, and OACs are recommended for those with an estimated risk of stroke or thromboembolic events of 2% or greater per year. Early rhythm control using AADs or catheter ablation is recommended in select patients with AF who have symptomatic paroxysmal AF or HFrEF.

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Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

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