REVIEW

MAYO CLINIC

The State of the Art: Atrial Fibrillation Epidemiology, Prevention, and Treatment

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Abstract

As the most common sustained arrhythmia in adults, atrial fibrillation (AF) is an established and growing epidemic. To provide optimal patient care, it is important for clinicians to be aware of AF's epidemiological trends, methods of risk reduction, and the various available treatment modalities. Our understanding of AF's pathophysiology has advanced, and with this new understanding has come advancements in prevention strategies as well as pharmacological and nonpharmacological treatment options. Following PubMed and MEDLINE searches for AF risk factors, epidemiology, and therapies, we reviewed relevant articles (and bibliographies of those articles) published from 2000 to 2016. This "state-of-the-art" review provides a comprehensive update on the understanding of AF in the world today, contemporary therapeutic options, and directions of ongoing and future study.

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Atrial fibrillation (AF) is the most common sustained arrhythmia in adults, and its prevalence is expected to increase 3-fold in the next 3 decades. Experts now characterize these epidemiological trends as an AF epidemic. On the basis of these considerations and multiple advances in prevention and treatment, all clinicians should be aware of the current management of AF. The therapeutic strategies for rate control or rhythm control have evolved considerably. The risks and benefits of anticoagulant therapy have a more robust evidence base to guide decision making about anticoagulation. At the same time, options for stroke prevention have evolved into novel pharmacological and nonpharmacological options. There is an important and growing body of evidence that the burden of AF can be reduced with lifestyle interventions that result in weight loss. Following PubMed and MEDLINE searches for AF risk factors (RFs), epidemiology, and therapies, we reviewed relevant articles (and bibliographies of those articles) published from 2000 to 2016. This "state-of-the-art" review represents a comprehensive update for all clinicians, which will ultimately serve to improve outcomes in patients with AF.

EPIDEMIOLOGY AND POPULATION TRENDS

Using Einthoven's string galvanometer in 1909, Lewis[1] and Rothberger[2] separately established electrocardiographically that "auricular fibrillation" caused "pulsus irregularis perpetuus," a condition that was noted years before by the Scottish cardiologist Sir James Mackenzie[3] to have lost the jugular A wave on his ink-writing polygraph. Initially thought of as an insignificant condition, AF is now recognized to have a substantial effect on morbidity and mortality, along with an increasing burden on health care utilization and cost.[4,5] AF is the most common clinically important arrhythmia, with a recent worldwide estimate of up to 33.5 million patients (not even including those with clinically silent disease), and is increasing in prevalence, making this a global epidemic.[6]

The epidemiology of AF is more clearly established in Western developed countries than it is in developing nations.[7,8] However, it appears that the incidence of AF in developed countries is twice as much as that in developing countries.[6] The estimated prevalence in the United States is around 5.2 million, with an expected increase to 12.1 million by the year 2030.[9]

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Age

Age is a major RF for AF, with the risk of developing AF doubling with each decade of life.[10] For example, in the Framingham population, the annual incidence of AF per 1000 persons for those younger than 65 years is 1.9 in women and 3.1 in men as compared with 31.4 in women and 38 in men among those older than 85 years.[11] In both men and women older than 40 years, the lifetime risk of AF in the Framingham population was estimated to be around 25%.[12] Similar findings were noted in a European cohort, with an incidence of AF of 1.1 per 1000 person-years in patients aged 55 to 59 years, increasing to 20.7 per 1000 person-years in those older than 80 years, with a lifetime AF risk comparable to that seen in the Framingham cohort.[13] According to a Medicare database review, the incidence of AF has remained approximately stable in the US population older than 65 years over the past decade, ranging from 27.8 to 28.3 per 1000 person-years.[14]

Race

In the United States, whites appear to have a higher risk of incident AF than do African Americans, Hispanics, and Asians.[15] An apparent paradox is evident in the lower incidence of AF in African Americans than in whites, despite African Americans' higher prevalence of RFs for AF.[8,16] The Cardiovascular Health Study was the first to suggest this paradox, with a 79% lower risk of AF in the African American population of the study.[17] The Analysis of the Atherosclerosis Risk in Communities (ARIC) study[16] also suggested that African Americans were at a lower risk of developing AF, with a 41% lower adjusted risk of developing AF compared with whites. A meta-analysis[18] of 10 studies examining more than 1 million patients reported that African American race appeared to be protective from AF, exhibiting a 49% lower risk. To further investigate whether genetic or environmental factors contributed to this AF paradox in African Americans, Marcus et al[19] used genetic analysis to determine the degree of European ancestry in African Americans in the Cardiovascular Health Study and ARIC study and correlated this information with the risk of developing AF. Interestingly, they found that for every 10% increase in European ancestry there was a 10% increased risk of incident AF.

ARTICLE HIGHLIGHTS

- Atrial fibrillation (AF) is an established and growing global epidemic.
- Several risk factors for AF have been identified, and risk reduction is possible through modification of these factors.
- The chief strategies for AF treatment—rate control and rhythm control—are both viable and have different advantages and disadvantages.
- Prevention of stroke and systemic embolism, a major aspect of AF treatment, is evolving in the form of new anticoagulant agents and left atrial exclusion techniques.
- Sinus rhythm maintenance may be accomplished through the use of antiarrhythmic drugs and/or ablative techniques.
- Rhythm control via ablation for AF, most often in the form of pulmonary vein isolation, is constantly improving and now includes procedures that are catheter-based, operative, or hybrid.

Sex

Sex also affects the incidence and effects of AF. For example, women have been found to be more symptomatic from AF and have longer paroxysmal AF episodes as well as faster ventricular response rates.[20] In the ARIC study,[16] women had a 46% lower risk of AF than did age-matched men. This difference was also seen in a Medicare database review from 1993 to 2007, in which men had an incidence of newly diagnosed AF of approximately 35 per 1000 person-years as compared with approximately 25 per 1000 person-years in women.[14] However, over that 15-year time period, the incidence of AF more than doubled for both sexes, which was related to the advancing age of the population. Despite their lower incidence of AF, it is well established that in the presence of AF, women have a higher risk of stroke than do men.[21,22] Furthermore, in the Copenhagen City Heart Study,[22] a population-based prospective cohort study, women appeared to have an independent 2.5-fold increased risk of cardiovascular (CV) mortality related to AF as compared with men.

COMORBID CONDITIONS AND MODIFICATIONS DESIGNED TO REDUCE AF RISK

The genesis and evolution of AF in any 1 patient involves many complex and as yet incompletely understood mechanisms. We do know that there are several important comorbid conditions that promote the development and maintenance of AF. Understanding potential contributors to AF is an important area of research that may translate into better treatment and prevention. Some of the most well-described modifiable factors that increase risk of AF are congestive heart failure (HF), hypertension (HTN), diabetes mellitus (DM), obesity, alcohol consumption, and obstructive sleep apnea (OSA).[23] Risk factor modification can affect the development and severity of AF, as illustrated in Figure 1 and discussed below.

Congestive HF

In his 1997 Shattuck lecture, Braunwald[24] predicted that AF and congestive HF would become epidemics in the 21st century. Atrial fibrillation and congestive HF often occur in the same individuals and share many comorbidities.[25] Atrial fibrillation itself is associated with up to a 3-fold increase in the risk of incident HF.[26] In the international Real-life global survey evaluating patients with Atrial Fibrillation,[27] the prevalence of congestive HF was associated with increasing persistence of AF (33% of those with paroxysmal AF had congestive HF, compared with 44% in those with persistent AF and 56% in those with permanent AF). Regardless of whether systolic function is preserved or reduced, the prevalence of AF is directly associated with New York Heart Association (NYHA) functional class: less than 10% in NYHA functional class

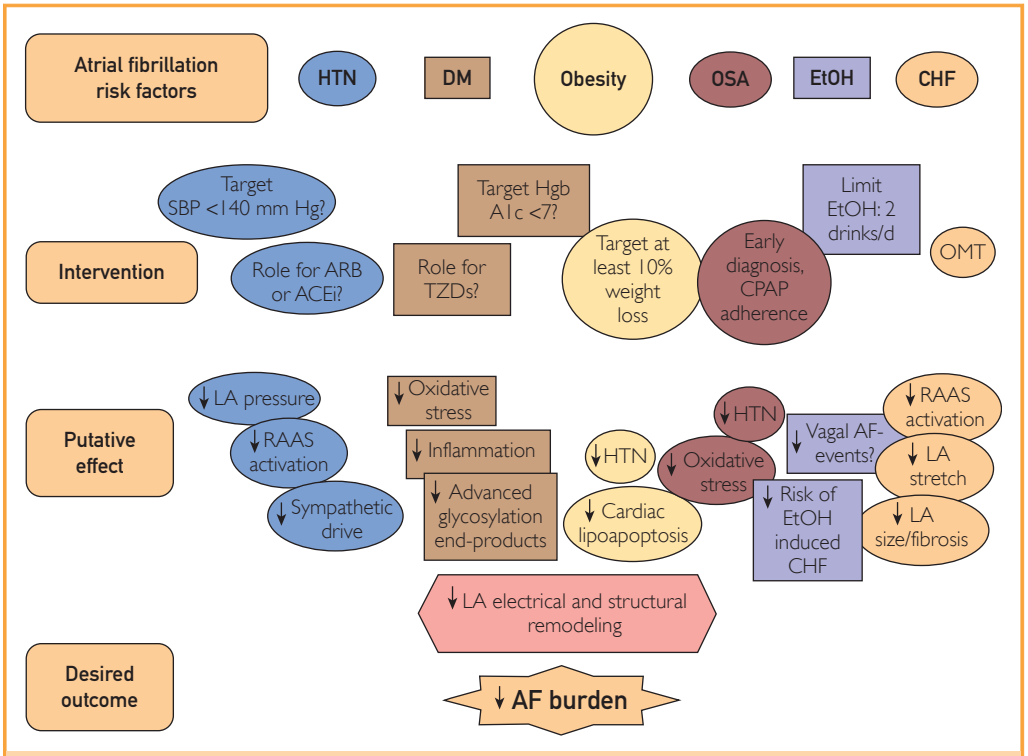


FIGURE 1. Atrial fibrillation risk factor modification and its putative effects. ACEi = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CHF = congestive heart failure; CPAP = continuous positive airway pressure; DM = diabetes mellitus; EtOH = ethyl alcohol consumption; Hgb A1c = hemoglobin A_{1c}; HTN = hypertension; LA = left atrial; OMT = optimal medical therapy; OSA = obstructive sleep apnea; SBP = systolic blood pressure; TZD = thiazolidinedione; RAAS = renin-angiotensin-aldosterone system.

I have AF compared with up to 55% in NYHA functional class IV.[28]

Importantly, patients with combined AF and congestive HF have a worse prognosis than those with either component alone. In an analysis[29] of the Framingham population, development of congestive HF in patients with AF was associated with increased mortality in both men (hazard ratio [HR], 2.7; 95% CI, 1.9-3.7) and women (HR, 3.1; 95% CI, 2.2-4.2). Conversely, in those with congestive HF, the subsequent occurrence of AF was associated with increased mortality in both men (HR, 1.6; 95% CI, 1.2-2.1) and women (HR, 2.7; 95% CI, 2.0-3.6).[29] A meta-analysis[30] reviewing prognosis among patients with congestive HF found an adjusted AF-related increase in mortality in 30,248 subjects from randomized controlled trials (odds ratio [OR], 1.4; $P<.0001$) and in 23,721 subjects from observational studies (OR, 1.14; $P<.05$).

Atrial fibrillation and congestive HF are mutual co-conspirators that induce complex structural, electrophysiological, and neurohormonal changes leading to their reciprocal evolution and perpetuation. Experimental models have shown that heterogeneity of repolarization throughout the atria, slowed atrial conduction, and a shortened atrial refractory period can cause and sustain AF.[31,32] Congestive HF induces atrial tissue stretch by way of increased atrial pressure and volume, leading to increased triggered activity and changes in refractoriness, predisposing to AF.[33] Furthermore, increased atrial automaticity and heterogeneity of depolarization and repolarization result from atrial hypertrophy and chamber enlargement.[34] Neurohormonal changes occurring in congestive HF via renin-angiotensin-aldosterone system (RAAS) activation promote extracellular matrix fibrosis, leading to heterogeneity of atrial repolarization and predisposing to the development of AF.[32,35] Angiotensin II may also increase the activity of pulmonary vein (PV) cardiomyocytes, which may lead to AF initiation.[36] Atrial fibrillation itself may lead to RAAS activation and may induce tachycardia-mediated cardiomyopathy, again exemplifying the complex interplay between AF and congestive HF.[37]

Hypertension

Numerous studies have implicated HTN as an independent RF for incident AF. For example, an analysis[10] of the Framingham cohort indicated that HTN independently increased the risk of AF by factors of 1.5 in men and 1.4 in women. Even pre-HTN range blood pressure has been associated with an increased risk of AF: the Women's Health Study suggested that the risk of incident AF during their 12.4 years of follow-up was greater in those with a baseline systolic blood pressure of 130 mm Hg or higher or a diastolic blood pressure of 90 mm Hg or higher.[38] Similar findings were noted in a cohort of middle-aged men followed for 35 years, in which baseline systolic blood pressure of 128 mm Hg or higher and diastolic blood pressure of 80 mm Hg or higher was associated with a 1.5-fold and 1.79-fold higher risk of incident AF, respectively.[39] Hypertension is believed to increase sympathetic output, increase left atrial pressure and volume, and activate the RAAS, thereby leading to atrial fibrosis, structural and electrical atrial remodeling, and promotion of AF.[40]

Conceivably, aggressive treatment of chronic HTN could help to reduce the risk of AF, and there is some evidence to this effect. A post hoc analysis[41] of the standard vs aggressive blood pressure lowering arms of the randomized Action to Control Cardiovascular Risk in Diabetes trial indicated that targeting a systolic blood pressure of less than 120 mm Hg compared with the "standard" target of less than 140 mm Hg trended toward a lower incidence of AF, though this finding was not statistically significant.

The choice of antihypertensive agent may affect the incidence of AF. The effect of angiotensin converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) on the prevention of AF is one controversial example. A post hoc analysis of 2 large investigations of HTN treatment—the Losartan Intervention For End Point Reduction in Hypertension[42] and Valsartan Antihypertensive Long-Term Use (VALUE)[43] trials—suggested that ACEi or ARB therapy might reduce incident AF. In the Losartan Intervention For End Point Reduction in Hypertension trial,[42] which enrolled hypertensive patients

with left ventricular (LV) hypertrophy but without AF, therapy with losartan had similar efficacy in lowering blood pressure as atenolol, but was associated with a 33% reduced risk of new-onset AF (relative risk, 0.67; $P<.001$). In the VALUE trial,[43] valsartan was associated with a lower incidence of AF compared with amlodipine (unadjusted HR, 0.843; $P=.046$). However, a meta-analysis[44] evaluating the efficacy of ACEi or ARB therapy in preventing AF revealed a lack of efficacy in the HTN subgroup, which included 3 trials and 26,403 patients. It should be noted that this meta-analysis[44] did not include the VALUE trial, that only 2 of the 3 included studies evaluated new-onset AF, and that there was significant heterogeneity between the 3 studies. A Danish retrospective nationwide nested 1:1 matched study[45] of individuals with only HTN found that the use of ACEi or ARB as monotherapy was associated with a dramatically lower risk of incident AF as compared with the use of β-blockers (ACEi: HR, 0.12; 95% CI, 0.10-0.15; ARB: HR, 0.10; 95% CI, 0.07-0.14) or diuretics (ACEi: HR, 0.51; 95% CI, 0.44-0.59; ARB: HR, 0.43; 95% CI, 0.32-0.58), but not compared with the use of calcium channel antagonists. A recent meta-analysis[46] of 4 randomized controlled trials found the ARB telmisartan to be more effective than other antihypertensive drugs in reducing AF recurrence (HR, 0.54; 95% CI, 0.34-0.86). Overall, these data indicate a potential role for RAAS blockade in preventing AF and reducing its recurrence, though more studies are needed.

Diabetes Mellitus

Diabetes mellitus is found in up to 20% of patients with AF.[47] The hyperglycemia of DM is believed to contribute to oxidative stress, inflammation, and formation of advanced glycosylation end products (which infiltrate the myocardium, causing hypertrophy and interstitial fibrosis), all of which lead to electrical and anatomical remodeling of the left atrium (LA) and promotion of AF.[48]

Evaluation of the Framingham population implicated DM as an independent contributor to new-onset AF in both men (OR, 1.4; 95% CI, 1.0-2.0) and women (OR, 1.6; 95% CI, 1.1-2.2).[10] Moreover, the VALUE trial[49] indicated that those who were diagnosed with type 2 DM during follow-up had a nearly 50% increased risk of new-onset AF (HR, 1.49; 95% CI, 1.14-1.94). Likewise, a meta-analysis[50] including nearly 1.7 million patients from several case-control and cohort studies indicated a 40% increased risk of AF in patients with type 2 DM.

Currently, there are no convincing published data to support specific upstream therapy for AF prevention in patients with DM. However, a few reports implicate thiazolidinediones (TZDs) as agents that may be associated with AF risk reduction. Thiazolidinediones activate peroxisome proliferator—activated receptor gamma, which decreases peripheral insulin resistance in patients with type 2 DM. However, the use of these agents is limited by adverse effects such as weight gain, congestive HF, and potentially bladder cancer.[51] A nationwide population-based cohort study[52] in Taiwan evaluated 12,065 patients with type 2 DM and observed that the use of TZDs was associated with a 31% lower adjusted risk of new-onset AF. In addition, in their prospective cohort study of 150 consecutive patients with type 2 DM undergoing pulmonary vein isolation (PVI) for drug-refractory paroxysmal AF, Gu et al[53] found that the use of the TZD pioglitazone was associated with a higher rate of maintenance of sinus rhythm (SR) without antiarrhythmic therapy over nearly 23 months of follow-up (86% vs 71%; $P=.034$). Animal models suggest that TZDs may prevent electrical and structural atrial remodeling via their anti-inflammatory and antioxidant properties.[54]

Obesity

Like AF, obesity is a growing worldwide epidemic.[55] An association between increasing body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared) and AF is becoming clear. Obesity is associated with left atrial dilation,[56] which may be mediated via cardiac lipoapoptosis[57] and impaired autonomic balance.[58] Indeed, long-term follow-up in the Framingham Heart Study indicated a 4% increase in incident AF for each unit increase in BMI.[59] However, this association was no longer significant after adjustment for echocardiographic left atrial diameter, indicating that the link between AF and obesity may be mediated by left

atrial structural changes. Similar findings linking obesity with an increased risk of AF were observed in the Women's Health Study,[60] the ARIC study,[61] and various other community cohort studies.[62,63] The Long-Term Effect of Goal-directed weight management on an Atrial Fibrillation Cohort study[64] of overweight patients with paroxysmal and persistent AF evaluated the effect and magnitude of weight loss on the burden of AF. Remarkably, the Long-Term Effect of Goal-directed weight management on an Atrial Fibrillation Cohort study found a 6-fold greater probability of arrhythmia-free survival in patients with a durable weight loss of 10% or more than in those who lost less weight. Furthermore, the CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation trial[65] evaluated how respiratory fitness in obese individuals, defined as BMI of 27 kg/m^2 or more, affected the rate of AF recurrence. Three hundred eight obese patients with symptomatic AF underwent baseline exercise stress testing to determine peak metabolic equivalents, and baseline respiratory fitness levels were categorized as low (≤85%), adequate (86%-100%), or high (>100%) according to the percentage of predicted metabolic equivalents achieved. Subjects were offered a tailored exercise program. At final follow-up (~4 years), those with high cardiorespiratory fitness levels at baseline and those who achieved a fitness gain of 2 metabolic equivalents or more had significantly better arrhythmia-free survival with or without a rhythm control strategy than did those with lower baseline fitness levels who did not achieve fitness gains.

Recent interest has arisen about the role of epicardial fat (ie, adipose tissue between the myocardium and the visceral pericardium) and AF.[66,67] Epicardial fat can be evaluated via noninvasive imaging techniques, such as cardiac magnetic resonance and computed tomography (CT). Studies have observed an association between abundant epicardial fat and atrial myocardial adipocyte infiltration.[68] A CT analysis of subjects in the Framingham Heart Study[68] indicated that total epicardial fat, but not *para*cardial or intra-abdominal fat, was independently associated with AF (OR per SD increase in pericardial fat volume, 1.28; $P<.05$). Likewise, a separate study[69] of 300 subjects who underwent CT analysis indicated that total epicardial fat volume was associated with AF. Furthermore, the volume of epicardial fat was significantly higher in patients with persistent AF than in those with paroxysmal AF. Potential mechanisms linking epicardial fat and AF include fatty infiltration potentially leading to anisotropic conduction in the atria, profibrotic adipokines leading to remodeling, inflammation, and autonomic nervous system dysregulation.[70]

Alcohol Consumption

The association between alcohol consumption and AF is well established.[71-73] Alcohol intake is associated with depressed cardiac function, cardiac conduction abnormalities, and interatrial electromechanical conduction delay.[73] In 1 study,[74] alcohol consumption and increased vagal activity were found to be independent triggers for paroxysmal AF. These 2 mechanisms were found to coexist in some patients, raising the possibility of a vagally mediated mechanism through which consumption of alcohol increases AF risk. A 34% increased risk of AF was noted in Framingham participants who consumed more than 3 drinks/d.[75] Furthermore, a prospective cohort study[76] found that consuming more than 14 drinks/wk was associated with a 39% higher independent risk of AF, and a recent meta-analysis[77] evaluating the "dose-response" relationship between alcohol intake and AF found a 10% increase in the relative risk of AF for each drink per day beyond the low threshold of only 1 drink/d. On the basis of these data, limiting alcohol consumption could be a pertinent strategy for preventing AF.

Obstructive Sleep Apnea

Obstructive sleep apnea is estimated to exist in 4% of otherwise healthy adult women and in 9% of healthy men.[78] Repetitive hypopnea and apnea, in association with episodes of hypoxia and subsequent recovery, are associated with increased sympathetic drive and parasympathetic withdrawal, increased blood pressure, and activation of inflammatory mediators and reactive oxygen species, all of which may be associated with atrial arrhythmia induction.[79,80] Not unexpectedly, OSA is frequently associated with AF. Gami et al[81] prospectively evaluated 151 consecutive

patients presenting for electrical cardioversion for AF. Compared with 312 consecutive general cardiology patients without a history of AF, those with AF had a significantly higher prevalence of OSA, with an OR of 2.19 (P=.0006). Another study[82] revealed a prevalence of OSA of 81.6% in patients with persistent AF who were referred for polysomnography as compared with a prevalence of only 60% in matched subjects without AF.

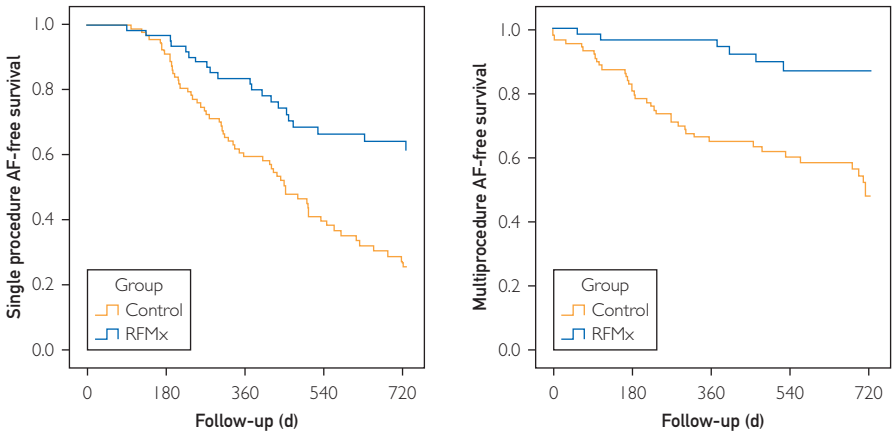
A synergistic effect between treatment of OSA and efficacy of AF therapies has been noted. Obstructive sleep apnea is associated with a higher AF recurrence rate after electrical cardioversion,[83] a lower rate of response to antiarrhythmic therapy,[84] and an increased risk of short-term recurrence of AF in patients undergoing PVI.[85] Several single-center studies have found that OSA therapy with continuous positive airway pressure (CPAP) reduces AF recurrence after electrical cardioversion[83] and improves the success rate of PVI.[86-88] In a large cohort study,[88] there was a dramatically lower rate of postablation AF recurrence in CPAP-treated patients than in patients with OSA who did not use CPAP (HR, 0.16; P<.001). Another observation of consecutive patients undergoing PVI, in which approximately 20% had OSA, noted that more than 42 months postablation, patients with OSA who were treated with CPAP had significantly less AF recurrence than did those with untreated OSA (35% vs 68%; P<.0001).[89]

Risk Factor Modification

Theoretically, intensive targeting of the myriad RFs for AF should reduce AF burden. This premise was tested in a randomized controlled trial[90] of 150 overweight or obese patients who underwent aggressive RF management with or without intensive weight management. The intervention group reported significant weight loss (14.3 kg vs 3.6 kg; P<.001), as well as markedly decreased AF frequency and symptomatic severity. Subsequently, the Aggressive Risk Factor Reduction Study for Atrial Fibrillation,[91] a single-center observational cohort study of consecutive patients with a BMI of 27 kg/m^2 or more and at least one other RF including HTN, impaired glucose tolerance or DM, hyperlipidemia, OSA, smoking, or excessive alcohol consumption, evaluated the effect of weight management and control of other RFs for AF on long-term outcomes after AF ablation. Risk factor management goals in affected individuals included an initial weight loss goal of 10% body weight with a subsequent goal of achieving a BMI of 25 kg/m^2 or less, increased exercise activity, achievement of goal lipid levels, lifestyle modifications, medical therapy as indicated to maintain a glycosylated hemoglobin level of 6.5% or less, a target blood pressure of less than 130/80 mm Hg, use of CPAP if indicated for OSA, and counseling to achieve smoking cessation and reduction in alcohol intake to 30 g/wk or less. Sixty-one patients participated in the RF management program, whereas 88 patients did not. After catheter ablation (CA), all patients were evaluated every 3 to 6 months using a Holter monitoring and clinic visits. Participants in the RF management program achieved greater weight and blood pressure reduction as well as improved glycemic and lipid control. As shown in Figure 2, compared with control subjects, those in the RF management program had far superior arrhythmia-free survival over an average of 3.5 years after a single ablation procedure (32.9% vs 9.7%; P<.001) and also after multiple ablation procedures (87% vs 17.8%; P<.001). Interestingly, aggressive RF modification was also associated with cardiac structural improvements including a reduction in left atrial volume index, LV septal thickness, and LV end-diastolic diameter. Although these findings are promising, larger randomized controlled trials are needed to establish definitively the apparent benefit of aggressive RF modification programs for patients undergoing AF ablation.

ECONOMIC AND PUBLIC HEALTH EFFECT OF AF

Atrial fibrillation imposes a significant financial effect on public health. It is estimated to account for 1% of the United Kingdom's National Health Service budget and $16 to $26 billion annually in medical expenditures in the United States.[92-96] Compared with matched patients, AF is associated with an estimated incremental medical cost of $8705 per patient per year, including inpatient, outpatient, and pharmacy costs.[93] The bulk of the increased cost of AF includes



Time (d)	0	180	360	540	730
RFM	61	59	48	33	27
Control	88	79	51	28	16

0	180	360	540	730
61	55	46	32	25
88	72	51	36	23

FIGURE 2. Atrial fibrillation–free survival in the Aggressive Risk Factor Reduction Study for Atrial Fibrillation of adding aggressive risk factor modification to AF ablation. AF = atrial fibrillation; RFM = risk factor management. Reproduced from *J Am Coll Cardiol*,[91] with permission.

hospitalization, stroke, HF, and loss of economic productivity.[95,97] Furthermore, evaluation of the disability-adjusted life-year metric, a means of assessing the effect of chronic disorders combining information on premature death (ie, years of life lost) and disability caused by the chronic disorder (ie, years lived with disability),[95] indicated that over the 20 years spanning 1990 to 2010, the worldwide burden of disability-adjusted life-year loss attributable to AF increased from 54 to 65 per 100,000 person-years for men and from 39 to 46 per 100,000 person-years for women.[6] These increases reflect a growing global epidemic of AF that not only is an economic burden but also contributes to a growing disability burden.

PATHOPHYSIOLOGY OF AF

Electrocardiographically, AF is characterized by findings including the presence of irregular R-R intervals and the absence of distinct P waves.[98] Mechanically, the chaotic electrical activity of AF leads to ineffective atrial contraction as well as further structural (and electrical) changes in the atria, which themselves potentiate AF.[32,99] Our understanding of the exact mechanisms and pathophysiology of AF is evolving. Although a consensus in the field has not been reached, it seems unlikely that a single mechanism can be implicated in AF initiation and maintenance. Almost certainly, AF is the ultimate manifestation of multiple disease pathways.[99,100]

A significant development in the history of AF was the identification of focal AF "triggers," which usually consist of spontaneous depolarization of atrial cells. The most common anatomical sources of ectopic atrial beats that trigger AF are the atrial myocardial "sleeves" extending onto the PVs. These transient ectopic tachycardias initially decrease atrial electrical refractoriness, which promotes AF.[101] Later, with repeated firing and atrial remodeling, AF is able to sustain itself via reentry within heterogeneously conducting atrial tissue.[102,103]

Once AF is initiated, the mechanisms allowing its maintenance remain disputed. Among competing theories, the "multiple wavelet hypothesis" proposes that there are multiple independent reentrant wavelets that exist within the fibrillating atria.[104,105] Other theories include focal activity within cardiac ganglionic plexi and untethered macroreentrant activity in the form of small spiral

reentrant drivers, often termed *rotors*.[106] Some consider rotors to be analogous to the vortex of a tornado, giving rise to the surrounding storm of AF.

The mechanisms described above are likely involved in various stages of AF. For example, initially when AF is transient (or "paroxysmal"), triggered activity likely is the originating mechanism. It is widely observed in the electrophysiology community that if AF is left untreated, it becomes more difficult to suppress (ie, that "AF begets AF").[32] In later stages of AF, with ongoing structural and electrical changes in the atrium, more complex mechanisms contribute to AF persistence (ie, AF that continues until it is either chemically or electrically cardioverted) or permanence (ie, AF that is refractory to all treatments). Because of this shift in pathophysiology, treatment of symptomatic patients with paroxysmal AF often focuses on the suppression of triggers, whereas treatment of persistent AF incorporates substrate-based therapeutic strategies.[98,106]

As detailed above, established RFs such as HTN, ischemic CV disease, valvular heart disease, HF, obesity, and DM can predispose patients to AF. The mechanisms linking these RFs to AF include structural and electrical changes to the LA, which then promote AF. It is hypothesized that atrial histological remodeling can result from increased left atrial pressure and size.[107,108] Vulnerability to the development of AF correlates with atrial dilatation, which leads to connective tissue disruption and eventual interstitial fibrosis. These atrial histological alterations can result in slowed atrial conduction velocity, local heterogeneous conduction, and local block, creating an ideal substrate for AF.[35,109,110] Neurohormonal and electrical atrial remodeling may also occur, which may further encourage the development of AF. For example, the RAAS can play a contributory role in adverse remodeling via its proinflammatory and profibrotic properties.[111-113]

As AF progresses, altered calcium handling, including calcium leak from the sarcoplasmic reticulum, can lead to increased automaticity and may also adversely affect conduction velocity and tissue refractoriness.[114] Partly because of the increased inward calcium current that results from frequent myocyte depolarization, the atrial cell's compensatory response is to down-regulate L-type Ca^{2+} channels to lessen calcium overload. However, the reduction in the concentration of these channels has the untoward adverse effect of shortening action potentials, reducing refractoriness, and further promoting AF.[115]

Increasingly, evidence links AF to inflammation.[116-119] This relationship has been reported in the immediate period after cardiac surgery.[120] In addition, inflammatory markers, such as C-reactive protein levels, tend to be more elevated in patients with persistent AF than in those with paroxysmal AF.[121] Furthermore, higher C-reactive protein levels predict AF relapse after cardioversion and have been associated with an increased thromboembolic risk.[122]

Other factors involved in AF initiation and maintenance include heightened autonomic nervous system activity and the structural fibrosis associated with aging.[123] Both parasympathetic and sympathetic nervous systems have been implicated. Specifically, when Holter monitor recordings were analyzed in patients with paroxysmal AF, the initiation of AF often occurred after an increase in adrenergic (sympathetic) tone, followed by an abrupt parasympathetic predominance immediately before the initiation of AF.[124]

The autonomic nervous system can promote atrial electrical heterogeneity and is a potential trigger of atrial arrhythmias, including AF.[125] In patients with chronic AF, atrial autonomic remodeling, including increased atrial sympathetic nerve density, is often present.[126] Concomitantly, the parasympathetic system can contribute by producing spatially heterogeneous atrial refractoriness, promoting intra-atrial reentry and supporting AF maintenance.[127] In light of the evidence for autonomic involvement in AF, therapeutic applications of neuromodulation are being sought to decrease AF's occurrence and maintenance. Currently, ganglionated plexus ablation, renal sympathetic denervation, cervical vagal nerve stimulation, and biological therapies (including targets for G-protein autonomic effectors) are under active investigation.[125]

Thus, the development of AF can be a multifactorial process, including susceptibility

related to comorbidities that promote early atrial enlargement, conduction heterogeneity due to atrial fibrosis, inflammation, ion channel abnormalities, and autonomic remodeling.

RHYTHM CONTROL VS RATE CONTROL

Patients and their physicians must cooperatively make a decision to pursue either a "rate control" or a "rhythm control" strategy in the management of their AF.

The rate control strategy primarily uses atrioventricular nodal blockade (often with β-blockers, calcium channel blockers, and/or digitalis) to limit the rate of atrioventricular conduction. Every patient with newly detected AF should initially receive adequate ventricular rate control (as needed) regardless of the chosen chronic management strategy. A sustained rapid ventricular response to AF over even a relatively short time may lead to the development of tachycardia-mediated cardiomyopathy. Furthermore, significant congestive HF symptoms can occur in patients who sustain rapid ventricular rates, even in the absence of overt LV systolic dysfunction.[98,128]

The heart rate target for the rate control strategy has evolved over time. In 614 patients with permanent AF over at least 2 years of follow-up, the randomized prospective trial Rate Control Versus Electrical Cardioversion II[129] established that a lenient rate control strategy (goal resting heart rate, <110 beats/min) is as effective as a strict rate control strategy (goal resting heart rate, <80 beats/min). Although the composite end point of death from CV causes, hospitalization for HF, and stroke as well as systolic embolism, bleeding, and life-threatening arrhythmic events were similar in both groups, the lenient rate control group had far fewer total clinical visits than did the strict rate control group (75 vs 684; $P<.001$).

Once ventricular rate control is achieved in the short term, the decision must be made to continue the rate control strategy alone or to pursue SR restoration and maintenance, also termed the *rhythm control strategy*. Rhythm control can be achieved through medical antiarrhythmic therapy, electrical cardioversion, and/or invasive procedures that are either catheter- or surgery-based.[98,130,131] When deciding among strategies, patient-specific factors such as stage of AF (ie, paroxysmal, persistent, or permanent), symptoms, age, comorbidities, and patient preference should be considered. Experts seem to agree that a trial of rhythm control should be offered at the first presentation of AF.[98,132] This approach offers patients with a potentially reversible cause of AF (eg, hyperthyroidism, pericarditis, or infection) or those with an isolated episode of AF the chance for early control of the arrhythmia. If AF does relapse, the choice is either to continue with a simple rate control strategy or to embark on a rhythm control strategy if there was symptomatic benefit after restoration of SR. Particularly appropriate patients for the rhythm control strategy include those who are young (age, <50 years), those with "lone" AF, and those with significant symptoms despite rate control.[132,133]

Antiarrhythmic therapy for AF, whether alone or in conjunction with electrical cardioversion and/or ablation, is currently recommended only for symptom amelioration and improvement in quality of life.[98] This restriction exists in part because no mortality benefit to rhythm control has been established in randomized controlled trials. For example, the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study[134] was the largest randomized controlled trial to compare the rate control and rhythm control strategies, and found similar all-cause mortality at 5 years in the 2 groups (24% vs 21%; $P=.08$). Critics of the AFFIRM study have argued that the adverse effects and imperfect efficacy of available antiarrhythmic therapy potentially limited the benefit of rhythm control. Supporting this suspicion, a supplementary analysis of the AFFIRM study[134] reported a gross mortality benefit to rhythm restoration, but this effect was neutralized by an increase in mortality associated with antiarrhythmic drug (AAD) use. Even among patients with HF, there was no identified difference between the strategies in terms of overall survival, CV death, worsened HF, or stroke.[135] Similarly, in a study[136] of patients who developed new-onset AF after cardiac surgery, there was no difference between the randomized treatment strategies of rate control or rhythm control in terms of death or other serious adverse events. After discharge, the rate of freedom from AF was similarly high between the groups. Thus far, the rhythm control strategy including catheter-based therapy has not undergone

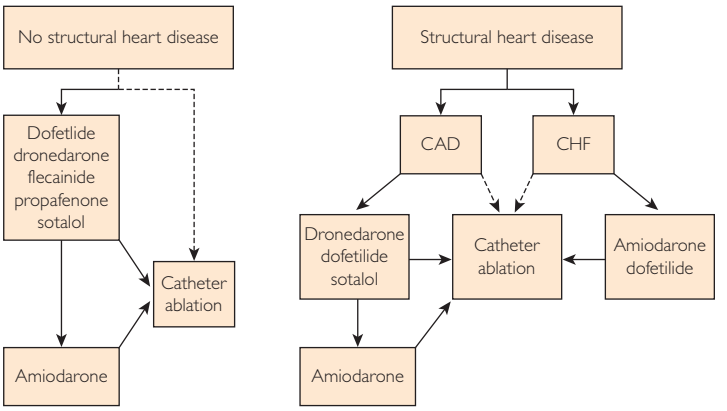


FIGURE 3. A candidate flow diagram for therapy for atrial fibrillation. For patients without structural heart disease, antiarrhythmic drug therapy with any agent except amiodarone is first-line therapy. Dronedarone, dofetilide, and sotalol are first-line agents for patients with CAD. Amiodarone and dofetilide are first-line therapy for patients with CHF. Amiodarone is a second-line agent for all patients without CHF. For patients with left ventricular wall thickness greater than 1.5 cm, only dronedarone and amiodarone are advised. Catheter ablation before antiarrhythmic drug therapy is a class IIa and IIb indication in patients with paroxysmal and persistent atrial fibrillation, respectively. CAD = coronary artery disease; CHF = congestive heart failure.

randomized controlled trials to assess its effect on mortality in any population.

Improvements in symptoms and quality of life may occur with rhythm restoration, but these benefits are not seen in all patients. However, after SR restoration there can be significant average symptomatic improvement.[133,135,137] For example, A Randomized Trial to Assess Catheter Ablation Versus Rate Control in the Management of Persistent Atrial Fibrillation in Chronic Heart Failure[138] found in 52 patients with symptomatic AF with LV ejection fraction less than 35% an objective improvement in exercise performance after PVI, including peak oxygen consumption (3.07 mL/kg per min; P=.02), improved Minnesota symptom scores, lower natriuretic peptide levels, and a trend toward improved 6-minute walk test (P=.10) after return to SR. Thus, a management strategy of rhythm restoration with either AADs or catheter-based ablation is appropriate in symptomatic patients with AF, despite a failure to show a clear mortality benefit. Finally, it should be mentioned that diminished *frequency* of AF can be seen as an acceptable outcome of the rhythm control strategy, rather than only accepting as success absolute AF suppression.

ANTIARRHYTHMIC DRUG THERAPY

For patients with symptomatic AF, AADs can be useful for improving symptoms via maintenance of SR. Also, for patients who develop cardiomyopathy related to rapidly conducted AF, AADs can be used to restore SR and thereby preserve LV function. In the acute setting, AADs can be used to facilitate successful electrical cardioversion. Antiarrhythmic drugs are not frequently used for patients with asymptomatic AF or for those with permanent AF. The success of AADs is often limited by contraindications to their use and by adverse drug effects.[139-141]

As summarized in Figure 3, the choice of AAD depends on the presence or absence of structural heart disease and/or HF, renal insufficiency, and LV hypertrophy (ie, LV wall thickness, ≥1.5 cm).[139] Class Ic agents, such as flecainide and propafenone, are restricted to those patients with structurally normal hearts and are contraindicated in patients with previous myocardial infarction.[142,143] Some class III agents, such as sotalol and dofetilide, are contraindicated in patients with creatinine clearance level less than 20 mL/min or baseline corrected QT interval greater than 440 ms.[142,144-146] Initiation of dofetilide requires 3 days of inpatient monitoring of the corrected QT interval, and similar inpatient monitoring for sotalol is recommended, but not mandatory.[145,146] Dronedarone is contraindicated in patients with advanced HF or a recent HF exacerbation.[147-151] Amiodarone and dofetilide are the only agents recommended for patients with LV dysfunction.[139,146]

Amiodarone is a second-line agent for most patients, but it remains widely used because of its high efficacy, its ability to be administered intravenously, and its applicability in patients with renal impairment and/or cardiomyopathy. Amiodarone has well-known toxicities including adverse effects on the lung, thyroid, liver, skin, and eye, requiring monitoring during long-term use. In addition, amiodarone has a higher risk of other adverse effects than do other AADs.[140]

The overall success rates of AADs for maintaining SR range between 30% and 50%, with amiodarone having the highest

efficacy.[139] For patients with drug-refractory symptomatic AF, procedural options are recommended (see below).

STROKE PREVENTION AND BLEEDING RISK

Risk Stratification for Stroke and Bleeding

Stroke and systemic embolism are significant causes of morbidity and mortality in patients with AF.[152,153] AF increases stroke risk 5-fold, and strokes that are related to AF lead to more severe disability and mortality.[153] For patients with valvular AF, especially AF related to mitral stenosis, the stroke risk can reach 20-fold that of a similar patient without AF.

Stroke prophylaxis in AF must balance a patient's thromboembolic risk with their bleeding risk. The most widely accepted risk stratification tools for stroke risk and bleeding risk are the CHA_2DS_2-VASc (Congestive heart failure, hypertension, age ≥75, diabetes mellitus, stroke, vascular disease, age 65-74, sex category [female]) and HAS-BLED (Hypertension, abnormal liver/renal function, stroke, bleeding risk, labile INRs, elderly (age ≥65), drugs/alcohol) scores, respectively (Table 1).[154,155] In addition to the original $CHADS_2$ score, the CHA_2DS_2-VASc score incorporates into the model age ≥65 years, female sex, and peripheral vascular disease. In addition to the CHA_2DS_2-VASc RFs, other known factors increasing stroke risk in patients with AF include spontaneous echo contrast, chronic kidney disease, and smoking.[156-158] The most recent AF guidelines advise oral anticoagulation (OAC) in patients at high risk (ie, CHA_2DS_2-VASc score, ≥2). For patients with moderate risk (CHA_2DS_2-VASc score, 1), the full gambit of possible prophylactic approaches (OAC, aspirin, or even no therapy) may all be considered, though expert opinion leans toward full anticoagulation (see below). For low-risk patients (CHA_2DS_2-VASc score, 0), the guidelines advise no antithrombotic therapy.[98] A HAS-BLED score of 3 or more predicts high risk of bleeding, but there are no available guidelines on therapy on the basis of this or any other bleeding risk algorithm.

TABLE 1. CHA_2DS_2-VASc and HAS-BLED Components, Scoring Methods, and Risk Calculators

CHA_2DS_2-VASc	Points	Score	Stroke risk
CHF	1	0	0%
HTN	1	1	1.3%
Age ≥75 y	2	2	2.2%
DM	1	3	3.2%
Stroke/TIA	2	4	4.0%
Vascular disease	1	5	6.7%
Age 65-75 y	1	6	9.8%
Female sex	1	7	9.6%
		8	6.7%
		9	15.2%

HAS-BLED (1 point each)	Score	Bleeding risk
Hypertension	0	0.9%
Abnormal Liver/Renal function	1	3.4%
Stroke	2	4.1%
Bleeding risk	3	5.8%
Labile INRs	4	8.9%
Elderly (age, ≥65 y)	5	9.1%
Drugs/alcohol	6-7	Too rare

CHF = congestive heart failure; DM = diabetes mellitus; HTN = hypertension; INR = international normalized ratio; TIA = transient ischemic attack.

In contrast to these epidemiological prediction scores, there also exist both temporal and structural determinants of stroke risk in AF. For example, the Asymptomatic Stroke and Atrial Fibrillation Evaluation in Pacemaker Patients (ASSERT) trial reported a roughly 2-fold increase in stroke rate for patients with atrial high rate episodes lasting for more than 6 minutes as detected by their pacemaker or defibrillator.[159] Interestingly, there was not a strong temporal association between AF events and strokes: only 6 of 59 patients with a stroke had an atrial high rate event detected within 30 days of their event.[159] In addition, the anatomy of the left atrial appendage (LAA) can predict the risk of stroke in AF, with more complex morphologies indicating higher thrombotic risk.[160]

Choice of Stroke Prophylaxis

For patients at high risk as well as in select patients with moderate risk, OAC therapy is advised for the reduction of stroke and systemic embolism.

Aspirin, Antiplatelet Agents, and Warfarin. Early trials examining stroke prevention in AF focused on warfarin and antiplatelet agents. Aspirin alone has exhibited essentially no meaningful effect on stroke reduction, with only the Stroke Prevention in Atrial Fibrillation (SPAF) trial reporting any

TABLE 2. Comparison of the Main Trials Leading to Novel Oral Anticoagulant Approval, Including Average $CHADS_2$ Score Among Subjects As Well As Hazard Ratios With 95% CIs for Stroke and Systemic Embolism, Major Bleeding, and Intracranial Hemorrhage[a,b]

Variable	RE-LY (N=18,113): dabigatran (150 mg bid)	ROCKET-AF (N=14,264): rivaroxaban (20 mg qd)	ARISTOTLE (N=18,201): apixaban (5 mg bid)	ENGAGE AF/TIMI 48 (N=21,105): edoxaban (60 mg qd)
$CHADS_2$ score	2.1	3.5	2.1	2.8
Stroke and systemic embolism	0.66 (0.53-0.82)[c]	0.88 (0.75-1.03)[d]	0.80 (0.67-0.95)[c]	0.88 (0.75-1.03)[d]
Major bleeding	0.93 (0.81-1.07)[d]	1.04 (0.90-1.20)[d]	0.69 (0.6-0.8)[c]	0.80 (0.71-0.91)[c]
Intracranial hemorrhage	0.40 (0.27-0.60)[c]	0.67 (0.47-0.93)[c]	0.42 (0.30-0.38)[c]	0.47 (0.34-0.67)[c]
Dose adjustment	75 mg bid if GFR 15-30 mL/min	15 mg qd if GFR 15-50 mL/min	Decrease dose to 2.5 mg bid if 2 or more of Cr >1.5, age >80 y, or weight <60 kg are present	30 mg qd if GFR 15-50 mL/min

[a]bid = twice daily; $CHADS_2$ = congestive heart failure, hypertension, age >75 y, diabetes mellitus, stroke, transient ischemic attack, or systemic embolism; GFR = glomerular filtration rate; qd = daily.

[b]Criteria for dose adjustments are also listed.

[c]Drug that met superiority criteria for the end point as compared with warfarin.

[d]Drug that met noninferiority criteria for the end point as compared with warfarin.

significant benefit.[161,162] Despite not having been studied in a low-risk population, because of its low risk, aspirin is an option for patients with a CHA_2DS_2-VASc score of 1 or less. In the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events - Aspirin (ACTIVE-A) trial,[163] the antiplatelet agent clopidogrel plus aspirin reduced strokes as compared with aspirin alone, at a cost of elevated bleeding risk. However, when clopidogrel and aspirin were compared with warfarin in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events - Warfarin (ACTIVE-W) trial,[164] warfarin produced a 40% further risk reduction of stroke and systemic embolism. Although warfarin is effective in reducing stroke rates, there are significant limitations to its use, including the need for frequent monitoring of the international normalized ratio, variable time in the therapeutic range (most often, target international normalized ratio, 2-3), the need for sometimes unacceptable dietary restrictions, and multiple drug-drug interactions. The recent advent of nonwarfarin oral anticoagulants has significantly increased treatment options.

Nonwarfarin Oral Anticoagulants (Novel Oral Anticoagulants/Direct Oral Anticoagulants). After more than 50 years of warfarin being the only OAC option, since 2010 4 nonwarfarin oral anticoagulants (also termed *novel oral anticoagulants* [NOACs] or *direct oral anticoagulants*) have been approved by the Food and Drug Administration (FDA) for stroke and systemic embolism reduction in nonvalvular AF.[165-168] A summary of the outcomes of the major trials leading to each NOAC's FDA approval is given in Table 2.

Dabigatran (Pradaxa), a direct thrombin inhibitor, was the first NOAC approved by the FDA, with the 150 mg dose studied in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial,[165] exhibiting superiority to warfarin therapy for stroke reduction (HR, 0.66; 95% CI, 0.53-0.82) as well as noninferiority for major bleeding (HR, 0.93; 95% CI, 0.81-1.07). In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation ARISTOTLE: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ROCKET-AF) trial,[166] rivaroxaban (Xarelto), a factor Xa inhibitor, exhibited noninferiority for reduction of stroke and systemic embolism (HR, 0.88; 95% CI, 0.75-1.03) as well as bleeding events (HR, 1.04; 95% CI, 0.90-1.20). Apixaban (Eliquis), a factor Xa inhibitor, is the only NOAC exhibiting superiority to warfarin for both stroke reduction (HR, 0.80; 95% CI, 0.67-0.95) and major bleeding (HR, 0.69; 95% CI, 0.60-0.80), as reported in the Apixaban for Reduction in Stroke and

Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial.[167] The Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation -Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial[168] studied edoxaban (Savaysa), the newest factor Xa inhibitor, and found noninferiority to warfarin for reduction of stroke and systemic embolism (HR, 0.88; 95% CI, 0.75-1.03) and superiority for reducing bleeding events (HR, 0.80; 95% CI, 0.71-0.91). All 4 NOACs exhibited statistically significant reduction in intracranial hemorrhage as compared with warfarin.

The choice of NOAC may depend on other factors in addition to efficacy and safety. The NOACs have variable dependence on renal clearance, sometimes leading to specific dose adjustments (Table 2). Only apixaban has been approved for patients on dialysis. Edoxaban is contraindicated in patients with robust renal function (glomerular filtration rate, >90 mL/min) because of rapid drug clearance. Of note, the only agent to exhibit superiority to warfarin for ischemic stroke prevention was dabigatran at the 150 mg dose twice daily.[165] Furthermore, only dabigatran has an FDA-approved reversal agent, idarucizumab.[169] The definition of "nonvalvular" AF was somewhat different across the various NOAC trials, but most often "valvular" AF included moderate to severe mitral stenosis, a prosthetic heart valve, or mitral valve repair. The only available study evaluating dabigatran use in the presence of mechanical heart valves, Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN),[170] reported *harm* in the dabigatran arm. To date, there has been no trial directly comparing NOACs.

As the individual NOAC trials included patients with a wide range of mean $CHADS_2$ scores, varying from 2.1±1.1 in the RE-LY and ARISTOTLE trials to 3.5±0.9 in the ROCKET-AF trial, caution must be exercised when drawing conclusions about these drugs' use in patients with much higher or much lower risk scores. Overall, the NOACs as a class exhibit favorable efficacy and safety profiles in comparison with warfarin. However, warfarin remains an effective agent for many patients, and it remains the only OAC approved for use in patients with prosthetic heart valves.

Left Atrial Appendage Closure

The most common site of intracardiac thrombus formation is the LAA.[171] Thrombi are particularly common in the LAA because of the LAA's dead-end anatomy and because of its prominent trabeculations.[172] Although OAC remains the principal method of preventing such thrombi, it does not completely eliminate stroke risk, and for some patients anticoagulation is contraindicated or undesirable. These limitations have generated increased interest in mechanical exclusion of the LAA as an adjunct to, or replacement for, OAC.

Surgical exclusion of the LAA is commonly performed at the time of other cardiac surgery, whether that surgery is solely targeted at AF treatment or is concomitant with other therapy (eg, mitral valve repair/replacement).[173] A number of approaches have been used for surgical exclusion. Surgical ligation with sutures or staples can be effective in some patients. However, when examined with transesophageal echocardiography, incomplete closure or nondurable occlusion has been found in a considerable number of patients.[174] Complete excision of the LAA appears to provide more effective results.[175] Newer technologies, such as the AtriClip external closure device (AtriCure Inc.), make surgical LAA closure technically easier than LAA amputation and oversewing and might be more effective than suture ligation.[176] Although minimally invasive approaches have been described, surgical LAA excision/closure therapies have the inherent disadvantage of being considerably invasive and are not routinely performed as stand-alone procedures.[175] In addition, available data on their effectiveness in stroke prevention are limited, though a large randomized controlled trial that seeks to provide more clarity is ongoing (https://clinicaltrials.gov/ct2/show/NCT01561651). On the basis of the available data, the 2014 AHA/ACC/HRS guideline for the management of patients with AF[98] provides a relatively weak consideration (class IIb; level of evidence C) for surgical exclusion of the LAA at the time of cardiac surgery.

Percutaneous therapies for LAA exclusion or closure have gained favor recently.[177,178]

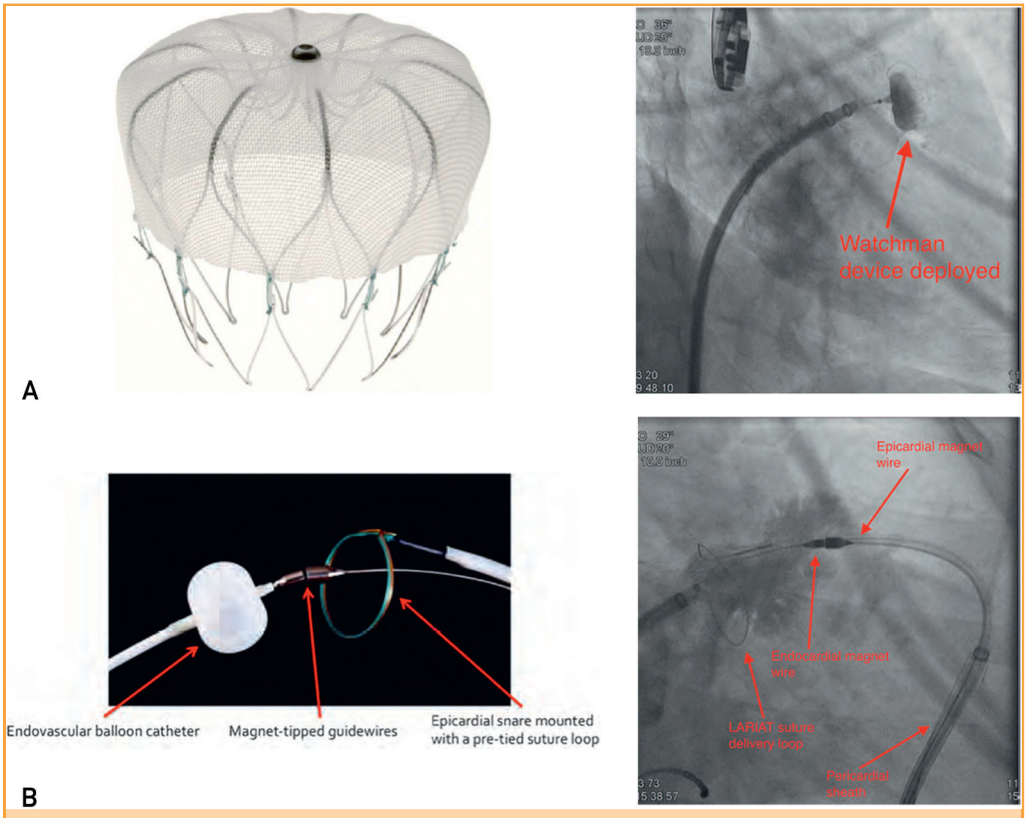


FIGURE 4. A, WATCHMAN device, which consists of a metallic frame with fixation barbs and a polyester fabric that covers the atrial face of the device, as well as a fluoroscopic image of a WATCHMAN device being deployed. B, LARIAT system, with its intracardiac (catheter/balloon/magnet) portion interacting with its epicardially delivered magnetic guidewire and preloaded catheter-delivered suture, as well as a fluoroscopic image just before LARIAT suture deployment. Reproduced from Prog Cardiovasc Dis[177] and Am Heart J[178] with permission.

Among these, the most promising technologies with supportive data are the intracardiac WATCHMAN LAA occluder (Boston Scientific) and the LARIAT system (SentreHEART Inc.), which cinches the LAA closed with a suture delivered epicardially. These devices are depicted in Figure 4.

The WATCHMAN device was examined in the Watchman Left Atrial Appendage System for Embolic Protection in Patients With Atrial Fibrillation (PROTECT-AF) trial,[179] which enrolled patients with AF who are warfarin eligible and compared LAA closure to OAC with warfarin and initially found LAA occlusion to be noninferior to OAC for stroke reduction (relative risk, 0.71; 95% CI, 0.44-1.3). Although there were concerns about procedure-related adverse events, with subsequent experience these events became less frequent, likely related to a considerable procedural learning curve.[180] With continued PROTECT-AF follow-up, the WATCHMAN device was more effective than warfarin for stroke reduction (HR, 0.61; 95% CI, 0.38-0.97) and similar in terms of safety.[181] Subsequently, the Prospective Randomized Evaluation of the Watchman LAA Closure Device In Patients With Atrial Fibrillation Versus Long Term Warfarin Therapy (PREVAIL) trial[182] and REgistry on WATCHMAN Outcomes in Real-Life Utilization (EWOLUTION) registry[183] confirmed WATCHMAN's high implant success rate and low risk. The WATCHMAN device is FDA approved for stroke risk reduction in patients who are warfarin eligible but for whom anticoagulation is undesirable.

In patients with a contraindication to warfarin, the WATCHMAN device has been

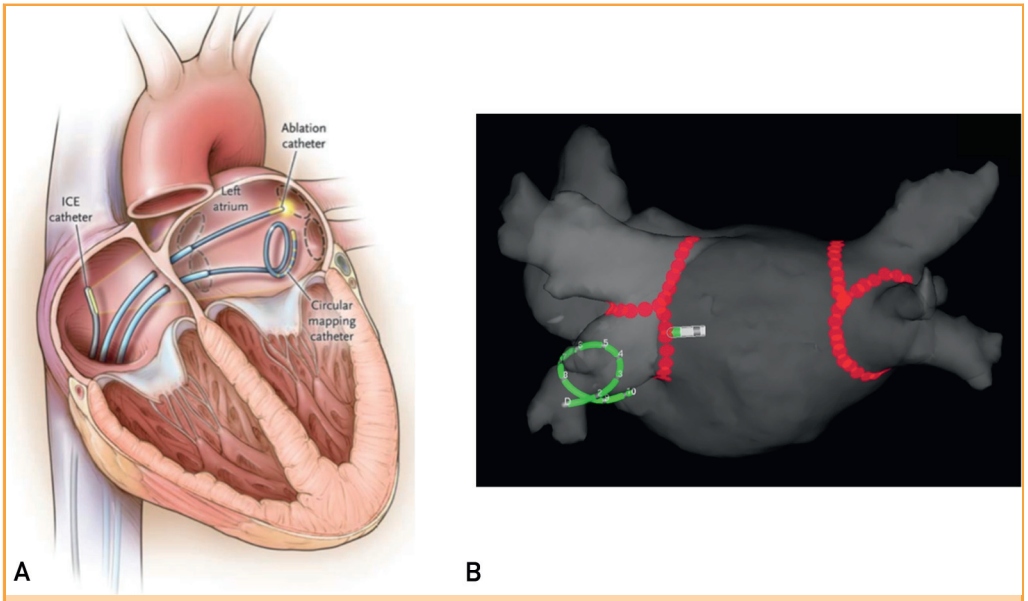


FIGURE 5. Pulmonary vein isolation using a standard radiofrequency catheter. A, Catheters that have been advanced from the femoral veins to the heart. An intracardiac echocardiography (ICE) catheter is positioned within the right atrium to guide transseptal puncture as well as mapping and ablation catheter manipulation. A circular mapping catheter is placed in each pulmonary vein and is used to assess for the presence of pulmonary vein potentials and to guide ablation. B, An electroanatomic map of the left atrium. Encircling ablation lesions (red) placed in a point-by-point fashion around the antrum of each pulmonary vein. A shadow of the circular mapping catheter is seen in the left inferior pulmonary vein with the tip of the ablation catheter (gray/green) delivering a lesion along the antrum of the vein. Panel A: Reproduced from N Engl J Med,[192] with permission.

found to be superior to historical controls, as well as cost-effective.[184,185] To date, no randomized study has been performed comparing WATCHMAN device and an inactive control. However, it seems likely that LAA closure may be useful for stroke prevention in OAC-contraindicated patients.

Originally marketed for use during laparoscopic procedures, the LARIAT suture/snare system is FDA approved for soft tissue closure. In thousands of cases, it has been used "off-label" to close the LAA via an epicardial approach. Its potential advantage over WATCHMAN is that LARIAT leaves no foreign material within the heart, which may lessen the need for even short-term postprocedure anticoagulation. Its weakness, however, may be the procedure's higher rate of significant procedural complications, as well as the risk of incomplete LAA closure.[186] A meta-analysis evaluating a total of 309 patients found a procedural success rate of 90%, with a rate of severe complications of 2.6%.[187] Similar to WATCHMAN, the LARIAT's rates of success and adverse events also show a significant learning curve[188]: in a more recent multicenter registry[189] of 682 patients, complete LAA closure was achieved in 98%, with a severe complication rate of only 1.6%. On follow-up, however, incomplete LAA closure was detected in approximately 7% of the examined patients.[189]

To date, published trials examining exclusion of the LAA have used warfarin as the active control. It remains unclear whether the future applicability of LAA closure will be affected by the superior efficacy and safety of the NOACs in comparison to warfarin.

ABLATION OF AF

Over the past decade, CA of AF has evolved considerably to become safer and more effective and is now among the most frequently performed cardiac procedures in the United States.[190]

As discussed above, PVs are the most frequent anatomical sources of ectopic atrial beats that can trigger paroxysms of AF.[191] Left atrial myocardial "sleeves" extending from the PVs are recognized as the primary source of triggers in 82% to 90% of patients with paroxysmal AF. Since the initial description of a PV trigger by Haissaguerre et al in 1998, electrical isolation of the PVs has been the primary end point in the catheter-based treatment of AF.[98,191]

In PVI, lesions are created in the LA, around the antrum of each vein, resulting in nonconducting scar. Most often, this is performed with catheters using radiofrequency energy to deliver point by point, connecting lesions around the circumference of the veins (Figure 5). Nonconducting tissue around the veins' antra then blocks electrical triggers from exiting (and entering) the veins, electrically isolating them from the LA and thus preventing the initiation of AF. The superiority of catheter-based PVI for the maintenance of SR compared to AAD therapy alone has been exhibited in several clinical trials and has driven the increase in ablation for the management of AF.[192-195]

Patient Selection for AF Ablation

The management of AF, including the use of CA, should be tailored to each specific patient, taking into account several factors including symptom severity and frequency, tolerance of medical therapy, age, and underlying comorbidities.[190] Patients and physicians should have a clear understanding of the goals of care, procedural risk, and realistic expectations of ablation outcomes. Although CA can be effective in individual patients, success rates have varied in clinical trials.

Early trials of CA focused on patients with paroxysmal AF and little or no structural heart disease who had failed medical therapy with at least 1 AAD. In these trials,[192-195] reported 12-month success rates ranged from 66% to 86%. It is clear that AF ablation is most successful in patients with paroxysmal AF.[196] Even so, many patients with paroxysmal AF require

TABLE 3. AHA/ACC/HRS Practice Guideline for the Management of Patients With Atrial Fibrillation: Recommendations for Catheter Ablation to Maintain Sinus Rhythm

Class I (Benefit >>> Risk; Procedure/treatment SHOULD be performed)
1. Atrial fibrillation catheter ablation is useful for symptomatic paroxysmal AF refractory or intolerant to at least 1 class I or III antiarrhythmic drug when a rhythm control strategy is desired. *(Level of evidence: A)*
2. Before consideration of AF catheter ablation, assessment of the procedural risks and outcomes relevant to the individual patient is recommended. *(Level of evidence: C)*
Class IIa (Benefit >> Risk; IT IS REASONABLE to perform procedure/treatment)
1. Atrial fibrillation catheter ablation is reasonable for some patients with symptomatic persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic drug. *(Level of evidence: A)*
2. In patients with recurrent symptomatic paroxysmal AF, catheter ablation is a reasonable initial rhythm control strategy before therapeutic trials of antiarrhythmic drug therapy, after weighing the risks and outcomes of drug and ablation therapy. *(Level of evidence: B)*
Class IIb (Benefit ≥ Risk; Procedure/treatment MAY BE CONSIDERED)
1. Atrial fibrillation catheter ablation may be considered for symptomatic long-standing (>12 mo) persistent AF refractory or intolerant to at least 1 class I or III antiarrhythmic drug when a rhythm control strategy is desired. *(Level of evidence: B)*
2. Atrial fibrillation catheter ablation may be considered before the initiation of antiarrhythmic drug therapy with a class I or III antiarrhythmic drug for symptomatic persistent AF when a rhythm control strategy is desired. *(Level of evidence: C)*
Class III (No benefit, or potential harm; Procedure/treatment IS CONTRAINDICATED)
1. Atrial fibrillation catheter ablation should not be performed in patients who cannot be treated with anticoagulant therapy during and after the procedure. *(Level of evidence: C)*
2. Atrial fibrillation catheter ablation to restore sinus rhythm should not be performed with the sole intent of obviating the need for anticoagulation. *(Level of evidence: C)*

AF = atrial fibrillation.
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TABLE 4. Randomized Controlled Trials of Catheter Ablation vs Antiarrhythmic Drug Therapy for the Management of AF[a]

Reference, year	Study design	Study size (N)	% of patients with paroxysmal AF	Freedom from AF recurrence			
				Follow-up	CA	AAD	*P* value
Krittayaphong et al,[200] 2003	CA as second-line therapy[b] compared to amiodarone	30	70%	1 y	79%	40%	.018
Wazni et al,[192] 2005 (RAAFT)	CA as first-line therapy	70	96%	1 y	87%	37%	<.001
Stabile et al,[201] 2005 (CACAF)	CA as second-line therapy	137	67%	1 y	55.9%	8.7%	<.001
Pappone et al,[193] 2006 (APAF)	CA as second-line therapy in paroxysmal AF	198	100%	1 y	93%	35%	<.001
Oral et al,[202] 2006	CA as second-line therapy in chronic AF	146	0%	1 y	74%	58%	.05
Jais et al,[194] 2008 (A4)	CA as second-line therapy in paroxysmal AF	112	100%	1 y	89%	23%	<.0001
Forleo et al,[203] 2009	CA as second-line therapy in patients with paroxysmal AF with type 2 diabetes	70	41%	1 y	80%	42.9%	.001
Wilber et al,[195] 2010 (ThermoCool)	CA as second-line therapy in paroxysmal AF	167	100%	9 mo (after a 3-mo blanking period)	66%	16%	<.001
Packer et al,[204] 2013 (STOP-AF)	Cryoballoon ablation as second-line therapy in paroxysmal AF	245	78%	1 y	69.9%	7.3%	<.001
Cosedis Neilsen et al,[205] 2012 (MANTRA-PAF)	CA as first-line therapy in paroxysmal AF	294	100%	2 y	85%	71%	.004
Morillo et al,[206] 2014 (RAAFT-2)	CA as first-line therapy in paroxysmal AF	127	98%	2 y	53%	41%	.03
Mont et al,[207] 2014 (SARA)	CA as second-line therapy in persistent AF	146	0%	1 y	70.4%	43.7%	.002

[a]A4 = Catheter Ablation versus Antiarrhythmic Drugs for Atrial Fibrillation; AAD = antiarrhythmic drug; AF = atrial fibrillation; APAF = Ablate and Pace in Atrial Fibrillation; CA = catheter ablation; CACAF = Catheter Ablation for the Cure of Atrial Fibrillation; CT = computed tomography; MANTRA-PAF = Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation; MRI = magnetic resonance imaging; NA = not applicable; RAAFT = Radiofrequency Ablation for Atrial Fibrillation Trial; RAAFT-2 = Radiofrequency Ablation versus Antiarrhythmic Drugs as First-Line Therapy of Atrial Fibrillation 2; SARA = Study of Ablation versus anti-aRrhythmic drugs in persistent Atrial fibrillation; STOP-AF = Sustained Treatment of Paroxysmal Atrial Fibrillation.

[b]"Second-line therapy" indicates AF recurrence despite previous management with at least 1 AAD.

more than 1 ablation procedure to produce durable success.[197]

Favorable success rates after CA in patients with paroxysmal AF have led to class I recommendations from the Heart Rhythm Society and the American College of Cardiology/American Heart Association Task Force on Practice Guidelines[98] for the use of CA to maintain SR in patients with symptomatic paroxysmal AF who are refractory or intolerant to at least 1 class I or class III AAD. Table 3 summarizes societal guideline recommendations for AF ablation. Despite the overall high levels of recommendation in support of ablation, it should be stressed that the decision to pursue ablation needs to be considered on a patient-by-patient basis, weighing individual factors as described above. In patients with more advanced AF and in those with substantial structural heart disease, the comparably lower success rates of ablation and the frequent need for recurrent procedures have led to lower levels of recommendation for ablation in patients with persistent AF and long-standing (>12 months) persistent AF (class IIa and class IIb, respectively).[98]

Patients with paroxysmal AF are more likely to achieve maintenance of SR than are those with either persistent or permanent AF.[198] For example, recent studies using catheter-based approaches in the treatment of paroxysmal AF have reported success rates of more than 80% at 1 year without antiarrhythmic medical therapy. In persistent AF, however, success rates are not as high, and ablation typically requires more extensive lesion sets to address the underlying atrial substrate. Among patients with persistent AF,

approximately 40% to 50% require a repeat procedure, after which the success rate approaches 70%.[199] Table 4 summarizes the results of several representative randomized controlled trials examining AF ablation.

Based on the present data, AF ablation should be limited to patients with symptomatic AF, with the goal of improving quality of life.[190] Although AF has been associated with an increased risk of stroke, HF, and death, the current evidence about whether CA reduces the risk of these outcomes remains insufficient.[26,29,134] Ongoing large multicenter randomized controlled trials will assess whether early CA reduces mortality and stroke risk as compared with noninvasive therapy with rate and rhythm control drugs.[208,209]

Innovations in Ablation Catheter Design

Atrial fibrillation ablation is most often performed via the femoral vein, with the LA being accessed via a transseptal approach. Intracardiac echocardiography can be used to guide transseptal puncture(s) and catheter placement within the LA.[210] Electroanatomic mapping systems are then used to create a computerized representation of the LA and the PVs.[210] Most commonly, a circular mapping catheter is placed within the PVs during ablation to record PV electrical potentials and assess for electrical isolation. An irrigated-tip radiofrequency ablation (RFA) catheter is then used to create point-by-point lesions encircling the antrum of each vein. Although ablation using a "simple" RFA catheter can be successful, it is not the current state of the art. Recent innovations in ablation catheter design have the intention of streamlining the procedure while also improving safety and efficacy. Some such advancements are depicted in Figure 6 and are discussed below.

Until recently, information on the quality of catheter-tissue contact existed only in the form of tactile feedback from the catheter, imaging (fluoroscopy and/or intracardiac ultrasound), and electroanatomic mapping. Recent data indicate that effective lesion formation depends on substantial contact force between the catheter and the tissue.[212,213] Consequently, novel RFA catheters have been designed to provide real-time information on the direction and magnitude of catheter-tissue contact force, allowing the operator to create more consistent lesions. The use of such catheters has been associated with reduced procedure time and decreased AF recurrence after CA.

One technical challenge in point-by-point PVI is the need for sustained periods of catheter manipulation by a skilled operator to create uninterrupted circumferential lesions. To mitigate this challenge, balloon-tipped catheters have been developed with the objective of creating contiguous lesions around the antrum of each PV.[214] In the most common current iteration of these procedures, the balloon is advanced toward the PV over an appropriately placed wire, wedging the balloon into the PV antrum. Through a central lumen, intravenous contrast is injected into the vein to evaluate for an effective seal of the PV, indicating circumferential balloon-tissue contact. The balloon is then filled with liquid nitrous oxide, producing tissue destruction via freezing (cryoablation).[214] Cryoablation using balloon-based catheters has proven effective in large clinical trials.[215,216] A recent randomized multicenter trial[217] compared cryoballoon ablation with point-by-point RFA in drug-refractory paroxysmal AF and found that the 2 techniques had similar efficacy and safety.

Another balloon-based catheter uses endoscopy to provide real-time direct tissue visualization and delivery of laser energy. In the first multicenter randomized trial[218] studying this technology, the visually guided laser balloon proved noninferior to standard radiofrequency PVI. Novel circular multipoint radiofrequency catheters have also been created and have been associated with short procedure times and high acute success rates.[211] Further research will be necessary to assess the long-term success of AF ablation using these innovative technologies.

Substrate Modification: Current and Emerging Strategies

The etiology of AF relapse despite confirmed PVI at the time of first ablation can be multifactorial. Possible causes for recurrence can include electrical reconnection of PVs, other (non-PV) anatomical sites functioning as triggers for AF, progression of atrial myopathy, and lack of sufficient arrhythmic substrate modification with PVI alone.[190,219] In contrast

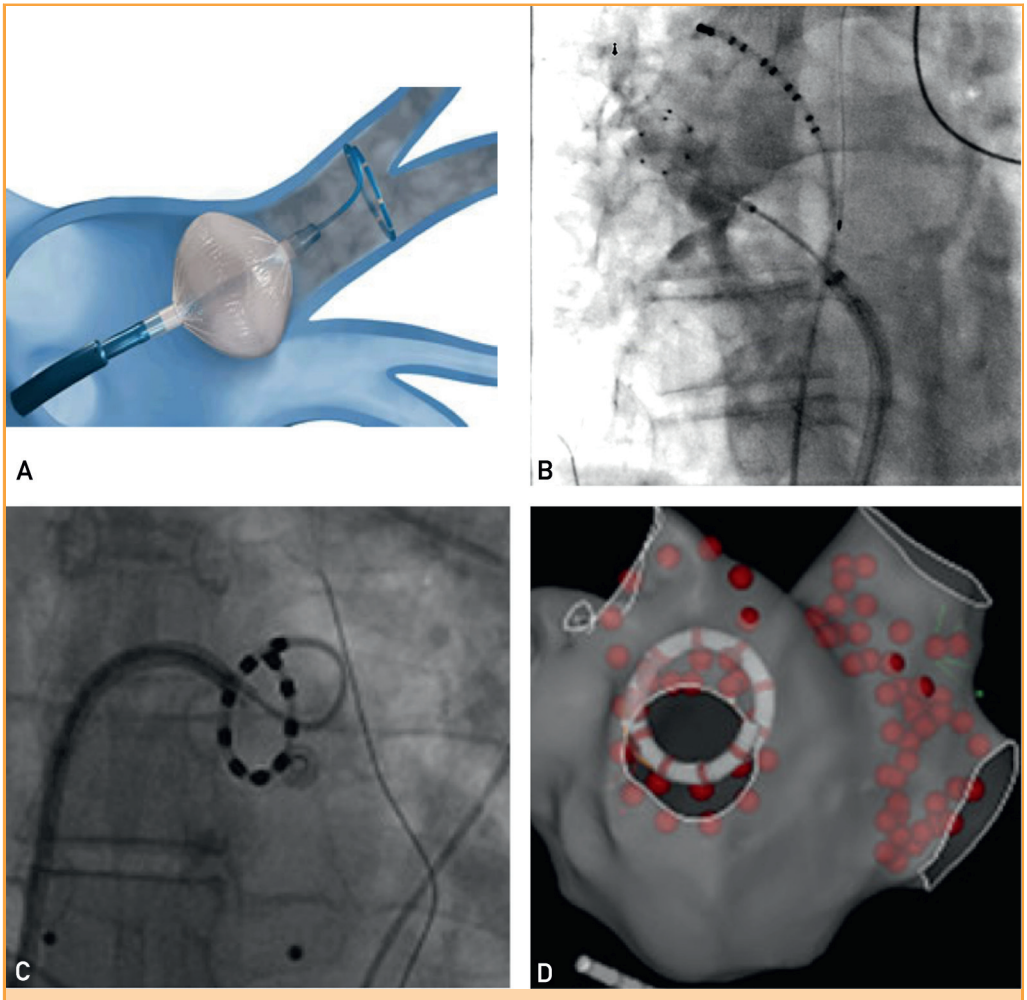

FIGURE 6. Novel strategies for pulmonary vein isolation. A, An artist's depiction of the cryoballoon. The balloon is inflated at the antrum of each pulmonary vein. Through a central lumen, a circular mapping catheter is placed within the vein to assess for pulmonary vein potentials. Through the same central lumen, intravenous contrast injections are used to evaluate for an effective seal of the pulmonary vein, indicating circumferential tissue contact around the antrum of the vein. B, A fluoroscopic image of the cryoballoon inflated in the antrum of the right superior pulmonary vein. A pacing catheter may be placed high in the superior vena cava, as shown here. Via that catheter, phrenic nerve pacing allows for monitoring of phrenic nerve injury during ablation of the right pulmonary veins. C, A fluoroscopic image of the nMARQ circular multipoint radiofrequency catheter placed in the antrum of the left inferior pulmonary vein. D, Three-dimensional left atrial anatomy with ablation lesions (red) created around each pulmonary vein and the nMARQ catheter in the antrum of the left inferior pulmonary vein. Panel A: Reproduced from https://www.medtronicacademy.com, with permission. Panel C and D: *J Cardiovasc Electrophysiol*. Reproduced from J Cardiovasc Electrophysiol,[211] with permission.

to most ablation procedures performed by cardiac electrophysiologists, in which the arrhythmic circuit or "*substrate*" is clearly identified and directly targeted for ablation (eg, the slow atrioventricular nodal pathway in atrioventricular nodal reentrant tachycardia or the cavotricuspid isthmus in typical atrial flutter), the appropriate target(s) for substrate modification in AF remain incompletely defined.

Over time, as PVI evolved from delivery of targeted lesions within the veins themselves to wide circumferential lesions enclosing the veins' antra, success rates have improved.[190,219] It is believed that moving

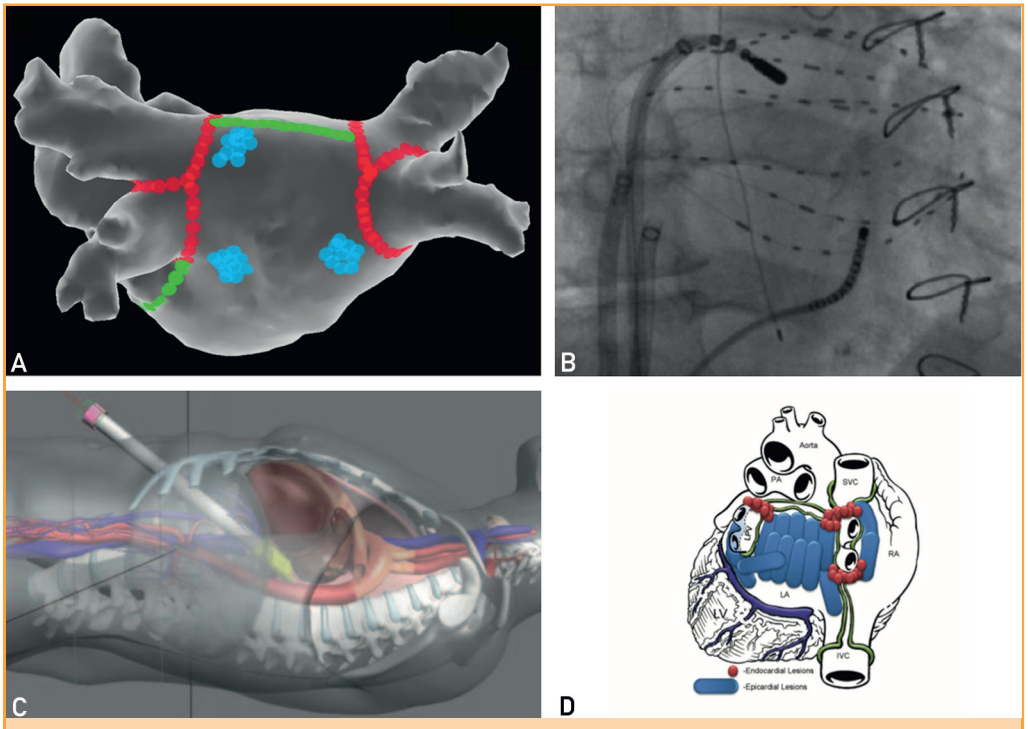

FIGURE 7. Strategies for substrate modification. A, A posterior view of the left atrium. Point-by-point ablation has been performed using standard radiofrequency catheter ablation. Pulmonary vein isolation lesions are shown in red. Additional substrate ablation has been performed with an anatomical "roof line" connecting the 2 superior pulmonary veins and a "mitral annular line" connecting the left inferior pulmonary vein and the mitral annulus (green lines). Areas of complex fractionated atrial electrograms have also been ablated (blue lesions). B, A fluoroscopic image of a 64-pole catheter placed in the left atrium to guide ablation of focal impulses and left atrial rotors. C, A minimally invasive subxyphoid approach for pericardioscopic epicardial ablation of the posterior wall of the left atrium. D, A representation of the lesions created by such an approach on the left atrial posterior wall. IVC = inferior vena cava; LA = left atrium; LPV = left pulmonary vein; LV = left ventricle; PA = pulmonary artery; RA = right atrium; SVC = superior vena cava. Panel B: Reproduced from *J Atr Fibrillation*,[221] with permission. Panel C: Reproduced from *Heart Rhythm*,[222] with permission. Panel D: Reproduced from *EP Lab Digest*,[223] with permission.

ablation sites into the body of the atrium results in further modification of AF substrate, contributing to this success. This theory is supported in studies performed in patients with previous AF ablation who remained free of clinical AF despite the identification of electrical reconnection in the PVs.[220] In many patients with paroxysmal AF, it appears that sufficient substrate modification occurs with antral PVI alone, but patients with more advanced disease—with persistent and longstanding persistent AF—may require additional ablation to achieve durable success.[190]

Because the optimal targets for substrate modification in nonparoxysmal AF remain unclear, several different ablation strategies have been examined. Some such techniques are depicted in Figure 7. One strategy attempts to emulate surgical approaches to "debulking" the LA by using RFA to create lines of block within the LA. The most commonly fashioned lines include a roof line connecting the left and right superior PVs and a mitral line connecting the left inferior vein to the mitral annulus.[224,225] Another strategy focuses on the mapping and ablation of complex fractionated atrial electrograms (CFAEs; pronounced "cafés") throughout the LA (and sometimes the right atrium).[226] It is believed that CFAEs might represent areas of slowed conduction or pivot points of wavelets that are critical in the maintenance of AF. The use of these techniques has shown mixed success in clinical trials, and over time, additional problems have

been recognized.[227] Gaps that result from anatomically noncontiguous lines or from nondurable lesions can result in recurrence of AF and can form the substrate for iatrogenic atrial flutters.[228] Mapping of CFAEs is relatively nonspecific, and 1 disadvantage of this approach is that extensive single point ablation can result in a proarrhythmic substrate.[227,229]

Mechanistic insights into AF have led to novel catheter-based techniques focusing on the identification and targeting of specific electrical substrates that could be central to the perpetuation of AF.[129] Despite the traditional description of AF as a disorganized rhythm, growing evidence points to focal impulses and organized sources of functional reentry, termed *rotors*, that might play a key role in the perpetuation of the arrhythmia.[230] A relatively novel strategy for AF ablation attempts to identify these localized, focal drivers of AF. The Focal Impulse and Rotor Modulation (FIRM) ablation technique uses a 64-pole "basket" catheter placed in the atria, together with a computational mapping approach, to identify localized rotors and focal impulses.[106] Targeting the electrical substrate using FIRM ablation in combination with PVI was more successful than conventional PVI alone in case series and early trials.[106,231] Randomized controlled trials assessing the short- and long-term success of FIRM ablation are ongoing.

Noninvasive mapping of rotors and focal impulses also has been described recently.[232] Electrical data obtained from a 252-electrode vest are combined with atrial anatomical geometry obtained from a cardiac CT scan to create a noninvasive map of AF drivers.[233] These data, obtained in the electrophysiology laboratory or just before ablation, can be used to guide electrical substrate ablation.[232] An ongoing prospective multicenter trial is investigating these techniques to guide localized electrical substrate ablation in patients with persistent AF.

There is some evidence supporting the notion that the substrate for AF stems from an underlying fibrotic atrial cardiomyopathy.[234] Using delayed enhancement magnetic resolution imaging, the degree of atrial remodeling can be quantified by identifying the total volume of atrial tissue fibrosis.[210] The extent and location of atrial fibrosis can vary, but on average it appears to be more advanced in patients with persistent as opposed to paroxysmal AF.[235] A multicenter prospective study found that in patients with AF undergoing CA, the degree of atrial fibrosis was independently associated with the likelihood of recurrent arrhythmia postablation.[236] The variability in the degree and distribution of fibrosis might help to explain why PVI can fail in patients with clinically paroxysmal AF but extensive atrial fibrosis and why PVI alone might be effective in some patients with persistent AF and only mild atrial fibrosis. Patients with a diffuse, extensive pattern of atrial fibrosis appear less likely to respond favorably to CA.[237]

Surgical and Hybrid Approaches to AF Management

The theory that the atrial substrate sustains AF by supporting multiple wandering electrical wavelets heavily affects the surgical approach to ablation. The objective of most surgical AF management is the creation of strategically fashioned lines of scar in an attempt to debulk the atrial substrate and interrupt the possibility of wavelet propagation.[219] A cut-and-sew technique known as the Cox maze procedure was first described in the late 1980s.[238] Subsequently, the procedure has evolved, with changes in the location of the lesion sets in the left and right atria, and replacement of incisional lesions with RFA and cryoablation.[238] Although success rates for surgical approaches to AF management can be high, because of the invasive nature of the procedure and the associated morbidity, a stand-alone surgical approach is infrequently used. Surgical ablation for AF is performed most often in patients undergoing concomitant cardiac surgery (eg, valve replacement) or in those symptomatic patients who have had 1 or more unsuccessful percutaneous CA procedures.[98]

Recently, a combined surgical and percutaneous approach, which has come to be known as *hybrid ablation* or the *convergent procedure*, has gained traction.[239] In hybrid ablation, a surgeon uses a closed-chest, minimally invasive approach to deliver transmural linear ablation lesions guided by direct visualization of the epicardial surface of the atrium. An electrophysiologist then performs percutaneous endocardial ablation, either immediately after the surgical ablation or at a later time (ie, in a "staged" approach). The addition of the

TABLE 5. Potential Complications of Catheter Ablation of Atrial Fibrillation

Complication	Prevention strategy	Symptoms	Management
Cardiac tamponade	Intracardiac echocardiography to guide transseptal puncture; use of contact force catheters to direct catheter manipulation	Hypotension; often abrupt	Percutaneous drainage and reversal of anticoagulation; if bleeding continues, surgical drainage and repair
Pulmonary vein stenosis	Avoidance of ablation within the pulmonary veins with targeted ablation toward the antrum	Dyspnea, chest pain, cough, hemoptysis, recurrent lung infections	CT or MRI if stenosis is suspected; for severe symptomatic stenosis, angioplasty or stenting of the pulmonary vein; surgery can be considered for restenosis
Vascular access complications			
Hematoma/retroperitoneal bleed Arteriovenous fistula Pseudoaneurysm	Meticulous access technique; ultrasound guidance can be helpful; careful manual compression postprocedure to achieve complete hemostasis	Groin/leg pain, swelling, pulsatile mass, hypotension, and shock if large retroperitoneal bleed	Manual compression of hematomas; pseudoaneurysm often managed with ultrasound-guided compression or ultrasound-guided local injection of thrombin; surgery might be required to manage large pseudoaneurysms, atrioventricular fistulas, or retroperitoneal bleed
Phrenic nerve injury	More common with ablation of right-sided (especially superior) pulmonary veins; avoid distal vein placement of cryoballoon or ablation catheter; phrenic nerve pacing during ablation to monitor for injury	Dyspnea, hiccups, cough	Nerve function usually recovers with time
Esophageal injury			
Atrial-esophageal fistula	Temperature probe for esophageal thermal monitoring; modifying energy delivery near the esophagus; use of proton pump inhibitor for several weeks postablation	Fever, chills, sepsis, neurologic events (septic emboli)	CT or MRI if suspected; urgent surgical correction or esophageal stent
Esophageal injury		Nausea, vomiting, bloating, abdominal pain	Usually recovers with time; small meals low in fat and fiber; rarely metoclopramide or other interventions needed
Stroke	Careful intra- and periprocedural anticoagulation management; heparin during ablation and oral anticoagulation for at least 2-3 mo postablation	Varying manifestations depending on the site of thromboembolism	Management based on severity and location of thromboembolism
Iatrogenic atrial flutter	Limiting ablation strategy to pulmonary vein isolation in paroxysmal atrial fibrillation; for additional ablation lines, electrical completeness of the line should be established by mapping or pacing maneuvers	Palpitations	Cardioversion; antiarrhythmic therapy; catheter ablation
Mitral valve injury	Careful manipulation of circular mapping catheters near the mitral valve to avoid entrapment and trauma	Symptoms can vary depending on the extent of trauma and underlying comorbidities	Gentle attempts to free catheter; echocardiography to confirm entrapment; surgical management/repair might be necessary

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TABLE 5. Continued

Complication	Prevention strategy	Symptoms	Management
Radiation injury	Minimizing fluoroscopy with the use of 3-dimensional mapping systems; adjustment of fluoroscopy frame rates	Acute or subacute skin burn	
Pericarditis	Minimizing extent of ablation when possible	Chest pain/pressure	Nonsteroidal anti-inflammatory drugs; colchicine; corticosteroids
Death	NA	NA	NA

CT = computed tomography; MRI = magnetic resonance imaging.

percutaneous approach to the surgical procedure allows for the direct electrophysiological assessment of isolation of the PVs and posterior LA, often with limited endocardial lesions necessary to achieve successful electrical isolation. In addition, any postsurgical atrial flutters can be targeted from an endocardial approach. Several centers have published their experience with hybrid ablation, reporting relatively high success rates, with most studies[240,241] including a fairly large proportion of patients with persistent and long-standing persistent AF. Although further study is needed to optimize patient selection and to assess clinical success, the hybrid ablation approach may provide an effective strategy for the management of AF in patients for whom 1 or more percutaneous attempts have failed. Hybrid procedures may also be useful for those with persistent or long-standing persistent AF, or for those with substantial structural heart disease, in whom standard CA techniques are unlikely to be successful.[239]

Future Directions

Although RFA has been used effectively for several decades, it does have limitations. Radiofrequency can cause collateral heat damage to tissues around ablation sites. In addition, the cooling effects of blood flow can limit lesion creation. Other ablation modalities are currently being explored, including nonthermal irreversible electroporation.[242] In porcine studies, a circular electroporation catheter has been used to create ablation lesions inside PVs. Compared with standard radiofrequency, electroporation lesions effectively ablated myocardial sleeves without causing surrounding connective tissue damage that can result in intimal proliferation, scar tissue formation, and ultimately PV stenosis.[243] Although further study is required, irreversible electroporation is a promising technology that might develop into an important modality for treatment of cardiac arrhythmias, including AF.[244]

Although CA has revolutionized the field of electrophysiology, it remains an invasive technique that can be associated with serious complications, which has stimulated exploration of alternative modalities. One such method currently under investigation is catheter-free radiotherapy. In animal models,

radiotherapy has been used for the noninvasive delivery of lesions to the heart,[245] and noninvasive carbon ion radiation for ablation of AF specifically is currently under investigation.[246] In the future, radiotherapy might offer a noninvasive approach for the management of cardiac arrhythmias, including AF.[247]

Practical Considerations

Atrial fibrillation ablation is often performed under general anesthesia, though some centers do use conscious sedation.[190] In most centers, patients after ablation remain under observation overnight and, barring any complications, are discharged the next morning.

Given the established periprocedural stroke risk, a careful anticoagulation strategy must be established before ablation. The usual practice is to rule out left atrial thrombus preprocedurally, most often via transesophageal echocadiography performed within 24 hours of ablation.[210] There also are data supporting the use of intracardiac echocardiography or cardiac CT to exclude thrombus.[248,249] The presence of left atrial thrombus is a contraindication to proceeding with ablation.

Standard practice during left atrial ablation includes continuous anticoagulation with heparin, and OAC is maintained for a minimum of 2 months postprocedure.[190] Data suggest that AF ablation can be more safely performed with uninterrupted therapeutic warfarin therapy, as opposed to periprocedural bridging anticoagulation with intravenous or low-molecular-weight heparin.[250] The periprocedural use of NOACs also has been used safely in some series.[251] Novel oral anticoagulants are often held the day of, and sometimes the day before, the procedure and reinitiated the night of ablation, after access site hemostasis has been confirmed.[98] Recent data suggest that ablation might be safely performed under uninterrupted NOAC therapy, though this is controversial.[252,253]

Ablation of AF should not be performed with the sole principal objective of discontinuing long-term OAC.[98] Standard practice dictates that postablation, long-term use of OAC is driven by individual risk of thromboembolism and bleeding, regardless of heart rhythm.[190]

Early postablation recurrence of AF is not uncommon, possibly because of indirect effects of cardiac ablation including myocardial inflammation and pericarditis. Although early recurrence of AF has been associated with a higher long-term arrhythmic risk, some such patients still show a favorable long-term response. For this reason, an early recurrence "blanking period" of 3 months has been used in most clinical trials, and recurrences during this time are not counted as procedure failures.[190] Patients should be made aware of the potential for early AF recurrence. Antiarrhythmic drugs taken before ablation is therefore often continued for 3 months postablation or may be instituted to suppress early recurrences in those previously not taking AADs.[98]

The most common cause of recurrence of AF (>3 months postablation) is reconnection of 1 or more PVs.[190] Although the decision to pursue repeat ablation after documented recurrence should be made on an individual basis, repeat procedures are associated with improvements in long-term success rates. Standard practice for repeat procedures is to reassess for electrical isolation of PVs and to reisolate veins with electrical reconnection. In patients without PV reconnection undergoing a repeat ablation procedure, targeting of non-PV triggers and substrate modification might be necessary.[190] Commonly observed non-PV triggers include the superior vena cava, coronary sinus, LAA, and other aspects of the LA including the posterior wall.[254]

As noted earlier, cardiac RFs such as obesity, OSA, HTN, and DM have been associated with atrial structural and electrical remodeling and an increased incidence of AF. Aggressive RF modification, including weight management, blood pressure control, OSA therapy, lipid and glucose control, and smoking and alcohol cessation can improve clinical outcomes. In a trial[91] assessing the effect of RF reduction on ablation outcomes, the aggressive RF reduction cohort exhibited marked improvements in ablation outcomes, with concomitant reductions in left atrial size and LVH. Patients should be educated on the importance of lifestyle and RF management as they relate to AF.

Although the safety of catheter-based AF ablation has improved with time, the procedure is associated with serious risks. Table 5 lists several potential complications of AF ablation.

An analysis of more than 93,000 procedures performed in the United States between 2000 and 2010 revealed an overall procedural complication rate of 6.3%.[255] Cardiac complications including tamponade were the most frequent (2.5%), followed by vascular (1.5%), respiratory (1.3%), and neurological (1.0%) complications. Advanced age and female sex have been associated with a higher adverse event rate.[98] Greater physician experience plays a role in reducing complications, with low hospital and operator volumes being associated with higher rates of adverse outcomes.[255]

CONCLUSION

Already an established global endemic, AF continues to grow in prevalence and importance. Our ability to cure this disease remains suboptimal, especially for patients with persistent and long-standing persistent AF. Recognition of the need to improve on contemporary practice has led physicians and scientists to more closely investigate the underlying mechanisms of AF. As our understanding of AF's epidemiology, pathophysiology, and therapeutic options continues to grow, it is expected that our ability to prevent stroke will improve, as will the efficacy and safety of ablation and other therapeutic options.

Abbreviations and Acronyms: **AAD** = antiarrhythmic drug; **ACEi** = angiotensin-converting enzyme inhibitor; **AF** = atrial fibrillation; **AFFIRM** = Atrial Fibrillation Follow-up Investigation of Rhythm Management; **ARB** = angiotensin receptor blocker; **ARIC** = Analysis of the Atherosclerosis Risk in Communities; **BMI** = body mass index; **CA** = catheter ablation; **CFAE** = complex fractionated atrial electrogram; **CPAP** = continuous positive airway pressure; **CT** = computed tomography; **CV** = cardiovascular; **DM** = diabetes mellitus; **FDA** = Food and Drug Administration; **FIRM** = Focal Impulse and Rotor Modulation; **HF** = heart failure; **HR** = hazard ratio; **HTN** = hypertension; **LA** = left atrium; **LAA** = left atrial appendage; **LV** = left ventricle/left ventricular; **NOAC** = novel oral anticoagulant; **NYHA** = New York Heart Association; **OAC** = oral anticoagulation; **OR** = odds ratio; **OSA** = obstructive sleep apnea; **PV** = pulmonary vein; **PVI** = pulmonary vein isolation; **RAAS** = renin-angiotensin-aldosterone system; **RF** = risk factor; **RFA** = radiofrequency ablation; **SR** = sinus rhythm; **TZD** = thiazolidinedione; **VALUE** = Valsartan Antihypertensive Long-Term Use

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