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# Atrial Fibrillation: Current Management and Best Practices

## INTRODUCTION

Atrial fibrillation (AF) is the most commonly diagnosed cardiac arrhythmia that results from structural or electrophysiological irregularities within the atrial tissue.<sup>1,2</sup> Unlike patients in normal sinus rhythm, those with AF have atria that contract rapidly (at approximately 400-600 beats per minute) leading to a heart rhythm commonly referred to as “irregularly irregular.”<sup>1</sup> As a result, the heart’s ability to pump blood may be impaired, leading to pooling of blood in the atria in those affected with AF. This pooling of blood puts them at an increased risk of both stroke and systemic embolism.<sup>2,3</sup>

In the United States, AF affects an estimated 2.7 million to 6.1 million people.<sup>4</sup> Its prevalence is projected to rise to more than 12 million by 2030 and to 15.9 million by 2050.<sup>4-7</sup> In men and women aged  $\geq 40$  years, the lifetime risk for developing AF is 1 in 4.<sup>8</sup> The projected increase can be attributed in large part due to the anticipated growth in the US population, but it also reflects the aging US population and improved survivorship.<sup>7</sup> One projection indicates that approximately 8 million of those affected by AF in 2050 will be aged  $\geq 80$  years.<sup>7</sup> Given the significant complications associated with AF such as stroke, heart failure (HF), tachycardia, and myocardial infarction, this will have substantial economic implications.<sup>4</sup>

Although multiple underlying risk factors and biomarkers exist for developing AF (Table 1)<sup>2</sup>, the most common risk factors include age greater than 60 years, diabetes, hypertension, coronary artery disease, prior myocardial infarction, HF, structural heart disease, prior open heart surgery, untreated atrial flutter, thyroid disease, chronic lung disease, obstructive sleep apnea, excessive alcohol or stimulant use, and serious illness or infection.<sup>2,9</sup>

Several longitudinal studies have clearly documented that AF carries an increased risk of morbidity and is an independent risk factor for death. The most serious and disabling complication is thromboembolic stroke; AF serves as an independent risk factor for stroke.<sup>7</sup> Estimates suggest that about 15% to 20% of US strokes can be attributed each year to AF.<sup>3</sup> In addition to being the fifth leading cause of death for men, and fourth for women, in the United States (Figure<sup>10</sup>), stroke is also a leading cause of serious long-term disability and is the leading preventable cause of disability.<sup>10,11</sup> While longitudinal studies have shown that individuals in their 50s with AF have a relatively low annual risk for stroke, the risk steadily climbs as a person ages. In patients aged  $\geq 80$  years, the relative risk of stroke has been shown to be as high as 23.5%.<sup>7</sup> HF is another negative outcome associated with AF. Estimates suggest 20% to 50% of AF patients will develop HF, and in patients with established HF, AF worsens outcomes.<sup>3,7</sup>

The financial impact of AF is significant; its US estimated incremental cost is \$26 billion annually. Of this amount, approximately \$6 billion is directly attributed to AF, with the remainder linked to other cardiovascular and noncardiovascular expenses.<sup>5</sup> In 1 evaluation of Medicare patients, when comparing those with AF to those without, AF patients had higher per-patient costs. In 2008, the excess cost in beneficiaries with AF was \$8705 greater than in those without.<sup>5</sup> About 75% of AF costs are related to direct and indirect costs associated with hospitalization. Claims data support the finding that the high costs attributed to hospitalizations are driven both by initial hospitalizations and frequent readmissions. One retrospective analysis showed that 42% of patients admitted with an initial diagnosis for AF or atrial flutter were readmitted within 1 year, with inpatient admissions driving more than half the direct costs. This amounted to \$22,579 in mean per-patient direct cost from January 2004 through December 2007. Other drivers of the overall cost include prescription drugs, testing, and care in the outpatient setting.<sup>7</sup> Additional financial burdens include the overall impact to society and lost productivity. While not often referenced in economic impact studies of AF, the condition contributes to increases in missed workdays and short-term disability.<sup>7</sup>

(Continued on page 6)

**TABLE 1.** Selected Risk Factors and Biomarkers for AF<sup>2</sup>

Clinical Risk Factors	Biomarkers
<ul style="list-style-type: none"> <li>• Alcohol use</li> <li>• Cardiothoracic surgery</li> <li>• Decreased left ventricular fractional shortening</li> <li>• Diabetes</li> <li>• European ancestry</li> <li>• Exercise</li> <li>• Family history</li> <li>• Genetic variants</li> <li>• Heart failure</li> <li>• Hypertension</li> <li>• Hyperthyroidism</li> <li>• Increased left ventricular wall thickness</li> <li>• Increased pulse pressure</li> <li>• Increasing age</li> <li>• Left atrial enlargement</li> <li>• Left ventricular hypertrophy</li> <li>• Myocardial infarction</li> <li>• Obesity</li> <li>• Obstructive sleep apnea</li> <li>• Smoking</li> <li>• Valvular heart disease</li> </ul>	<ul style="list-style-type: none"> <li>• Increased B-type natriuretic peptide</li> <li>• Increased C-reactive protein</li> </ul>

Adapted from January CT, Wann LS, Alpert JS, et al; ACC/AHA Task Force Members. *Circulation*. 2014;130(23):2071-2104. doi: 10.1161/CIR.000000000000040.

(Continued from page 1)

Stroke and HF, the key morbidities associated with AF, are the main contributors to AF's heavy economic burden. The American Heart Association estimates that overall US stroke-related costs in 2016 were \$33 billion.<sup>7,12</sup> Strokes in AF patients are typically more severe, exhibit greater morbidity, and lead to worse outcomes, so the overall economic burden to the healthcare system is disproportionately higher in this population. For instance, Lee and colleagues examined a randomized sample of Medicare beneficiaries versus a demographically matched control group, and excess treatment costs in the AF population averaged \$14,199 more than those of the control group. Additionally, stroke was determined to be as likely in the AF population. The same analysis indicated that incidence of HF was 3 times as likely in the AF group and also increased the total cost of care. In analyzing Medicare beneficiaries aged ≥65 years, Caro and associates developed an economic model to examine stroke in AF patients. The model predicted that, within 1 year, 96,980 strokes would occur, resulting in \$2.6 billion in direct costs incurred during the first year after the stroke.<sup>7</sup>

## MANAGEMENT OF ATRIAL FIBRILLATION

AF can be categorized into several different classifications characterized by duration of AF and the ability to convert to normal sinus rhythm.

The classifications include paroxysmal, persistent, long-standing persistent, permanent, and nonvalvular AF (NVAF) (Table 2).<sup>2</sup> A patient's classification can change after attempting new or different treatment strategies.<sup>13</sup>

Management of AF from a rate control or rhythm control perspective has been studied via a meta-analysis of 5 randomized trials.<sup>7</sup> Rate control in combination with anticoagulation as front-line treatment has been shown to be as effective as rhythm control. A follow-up cost-effectiveness analysis from the AFFIRM study showed savings in the rate control group based on less utilization of hospital days. The HOT CAFÉ study, along with its subanalysis, the RACE study, also demonstrated lower costs in rate control groups, primarily due to drug costs and the use of cardioversion in the rhythm control group.<sup>7</sup>

The decision to either restore normal sinus rhythm or control ventricular rate is crucial to AF management. The selected treatment approach should be based on the patient's clinical evaluation, including a detailed medical history, physical exam, echocardiography, and thyroid function tests, to rule out the presence of certain underlying factors that could render some treatments potentially harmful.<sup>13,14</sup> Management approaches for rate and rhythm control include pharmacologic therapy (Table 3); invasive electrophysiologic interventions such as electrical cardioversion, catheter-based ablation, and surgery.<sup>13,15</sup>

## PHARMACOLOGIC THERAPY

### Rate Control

The goal of pharmacologic therapy for rate control is to decrease the ventricular rate, both at rest and during exertion, without causing excessive bradycardia. Beta blockers, non-dihydropyridine (DHP) calcium channel blockers, and digoxin all have different mechanisms of action but the same effect on ventricular rate—conduction through the atrioventricular node is slowed down.<sup>14</sup> Of these 3 drug classes, beta-blockers are the most effective when used alone to achieve rate control. The AFFIRM study demonstrated that 70% of patients taking a beta blocker achieved their target heart rate goal, compared with 54% of patients taking a non-DHP calcium channel blocker.<sup>14</sup> Non-DHP calcium channel blockers, such as verapamil and diltiazem, are preferred for AF patients with preserved left ventricular systolic function and severe chronic obstructive pulmonary disease. Verapamil and diltiazem are equally effective to control ventricular rate.<sup>14</sup> The 2014 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) Guideline for the Management of Patients with AF recommends using a beta blocker or non-DHP calcium channel blocker to control ventricular rate in patients with paroxysmal, persistent, or permanent AF.<sup>2</sup> Less effective for achieving rate control is digoxin, a third option. Patients treated with pharmacologic therapy to achieve rate control may require the use of more than 1 drug.<sup>14</sup>

### Rhythm Control

The AHA/ACC/HRS guideline recommends treating AF with an antiarrhythmic drug, to maintain sinus rhythm. Once risks have been assessed (class I recommendation), choices include amiodarone, dofetilide,

dronedaron, flecainide, propafenone, and sotalol, depending on underlying heart disease and comorbidities.<sup>2</sup>

The most commonly prescribed antiarrhythmic drug for AF is amiodarone, even though it does not have FDA approval for this indication. Amiodarone is the most effective antiarrhythmic drug available; however, its use is limited by potential pulmonary, liver, and thyroid toxicities.<sup>16</sup> Amiodarone is only recommended after those toxicities have been taken into careful consideration, and after other antiarrhythmics have failed or been contraindicated (class I recommendation).<sup>2</sup>

Dronedaron has a similar structure to amiodarone; its use is associated with fewer noncardiovascular adverse events (AEs), and at the time of its FDA approval, it was believed to have been associated with a decreased stroke risk in AF patients.<sup>16</sup> However, further review led to the addition of an FDA black box warning of increased risk of death, stroke, and HF in patients with decompensated HF or permanent atrial fibrillation and other contraindications. Dronedaron must not be used in patients with symptomatic HF with recent decompensation requiring hospitalization, or with New York Heart Association Class IV HF; both, in combination with dronedaron, can increase the risk for death. It is also contraindicated in AF patients who will not or cannot be cardioverted into normal sinus rhythm. In patients with permanent AF, dronedaron doubles the risk of death, stroke, and hospitalization for HF.<sup>17</sup>

Flecainide and propafenone should be used in AF patients without structural heart damage. However, they are contraindicated in patients with prior myocardial infarction (MI) and reduced left ventricular function, because ventricular proarrhythmia may occur.<sup>16</sup>

Sotalol is a highly utilized antiarrhythmic drug, popular likely due to minimal noncardiovascular AEs associated with its use. Approach higher doses with caution, however, as they are associated with a higher risk of ventricular proarrhythmia.

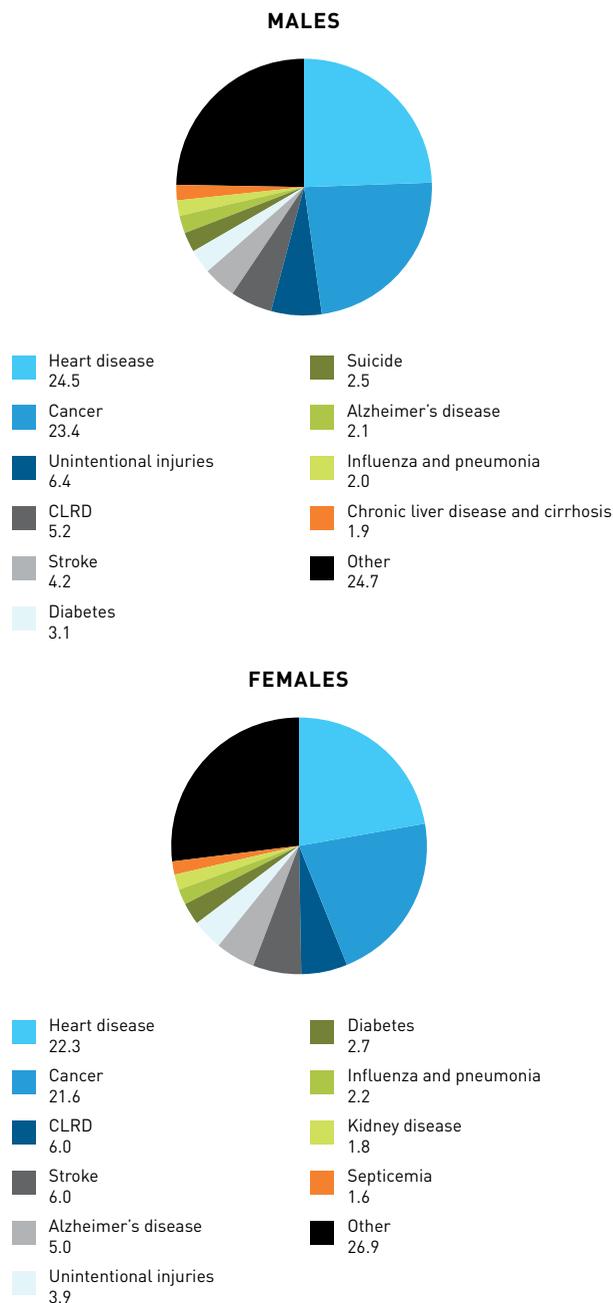
Dofetilide, although reasonably safe in HF and post-MI patients, is not widely utilized to maintain sinus rhythm.<sup>16</sup> The FDA has eliminated the Risk Evaluation and Mitigation Strategy criteria for dofetilide, but its use is still associated with serious ventricular arrhythmias; also, initiation requires an inpatient hospital stay.<sup>16,18</sup>

## Anticoagulation

In patients who are candidates for anticoagulation therapy, the AHA/ACC/HRS Atrial Fibrillation practice guideline provides warfarin with an international normalized ratio (INR) goal of 2.0 to 3.0, with dabigatran, rivaroxaban, and apixaban as treatment options (class I recommendation).<sup>2</sup> Warfarin, a vitamin K antagonist (VKA) oral anticoagulant, has been the gold standard for many years. However, non-VKA oral anticoagulants (NOACs) entered the market in 2010 and are increasingly preferred for certain patient populations.

Dabigatran etexilate is a prodrug which is converted by serum esterases to dabigatran.<sup>19</sup> This competitive direct thrombin inhibitor is approved to reduce the risk of stroke and systemic embolism in patients with NVAF.<sup>20</sup> In the RE-LY study, dabigatran 150 mg administered twice daily was associated with lower rates of strokes and embolism than observed with warfarin in patients with AF and a risk for stroke; however, rates of major bleeding were similar.<sup>21</sup>

**Figure.** Distribution of 10 Leading Causes of Death, by Sex, 2014<sup>a,10</sup>



CLRD indicates chronic lower respiratory diseases.

<sup>a</sup>Values show percentage of total deaths.

Rivaroxaban and apixaban, both NOACs, exert their anticoagulant effects via a different mechanism than that of dabigatran. These drugs work by directly inhibiting factor Xa in the coagulation cascade.<sup>22,23</sup>

The ROCKET AF trial demonstrated that when rivaroxaban was used in AF patients at moderate to high risk for stroke, the drug was found

**TABLE 2.** Classifications of Atrial Fibrillation (AF)<sup>2</sup>

Classification	Definition
Paroxysmal AF	Terminates spontaneously or with intervention in <7 days Recurrent episodes may occur
Persistent AF	Continuous AF duration >7 days
Longstanding persistent AF	Continuous AF duration >12 months
Permanent AF	Joint decision between patient and clinician not to pursue rhythm control treatment
Nonvalvular AF	AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair

Adapted from January CT, Wann LS, Alpert JS, et al; ACC/AHA Task Force Members. *Circulation*. 2014;130(23):2071-2104. doi: 10.1161/CIR.0000000000000040.

**TABLE 3.** Pharmacologic Management<sup>2</sup>

Rate Control	
Beta blockers	<ul style="list-style-type: none"> <li>• Atenolol</li> <li>• Bisoprolol</li> <li>• Carvedilol</li> <li>• Esmolol</li> <li>• Metoprolol succinate</li> <li>• Metoprolol tartrate</li> <li>• Nadolol</li> <li>• Propranolol</li> </ul>
Nondihydropyridine calcium channel antagonists	<ul style="list-style-type: none"> <li>• Diltiazem</li> <li>• Verapamil</li> </ul>
Digitalis glycoside	<ul style="list-style-type: none"> <li>• Digoxin</li> </ul>
Other	<ul style="list-style-type: none"> <li>• Amiodarone</li> </ul>
Rhythm Control	
Vaughn Williams Class IA	<ul style="list-style-type: none"> <li>• Disopyramide</li> <li>• Quinidine</li> </ul>
Vaughn Williams Class IC	<ul style="list-style-type: none"> <li>• Flecainide</li> <li>• Propafenone</li> </ul>
Vaughn Williams Class III	<ul style="list-style-type: none"> <li>• Amiodarone</li> <li>• Dofetilide</li> <li>• Dronedaron</li> <li>• Sotalol</li> </ul>
Anticoagulation	
Vitamin K antagonist	<ul style="list-style-type: none"> <li>• Warfarin</li> </ul>
Direct-acting oral anticoagulants	<ul style="list-style-type: none"> <li>• Apixaban</li> <li>• Dabigatran</li> <li>• Rivaroxaban</li> </ul>

Adapted from January CT, Wann LS, Alpert JS, et al; ACC/AHA Task Force Members. *Circulation*. 2014;130(23):2071-2104. doi: 10.1161/CIR.0000000000000040.

to be noninferior to warfarin for the prevention of stroke or systemic embolism. Fatal bleeding or bleeding at a critical anatomical site occurred less frequently than with warfarin; however, rivaroxaban patients had more gastrointestinal bleeding, bleeding leading to a decrease in hemoglobin level, and bleeding leading to the need for transfusion.<sup>22</sup> Apixaban, also a direct oral factor Xa inhibitor, was evaluated in the ARISTOTLE trial in AF patients with at least 1 other risk factor for stroke using a 5-mg twice-daily dose in most patients; fewer than 5% of patients received a lower dose. Apixaban demonstrated superiority over warfarin for the primary outcome of stroke or systemic embolism and reduced major bleeding by 31%.<sup>23</sup>

As demonstrated in the aforementioned studies, there are benefits to anticoagulating with NOACs. These include the lack of necessity for routine blood monitoring requirement and dose adjustments; fewer drug-food and drug-drug interactions than warfarin has; and lower rates of intracranial bleeding, compared with warfarin.<sup>24</sup>

In the past, clinicians were cautious about using NOACs because no reversal agent was available—idarucizumab, however, has changed that. Idarucizumab is a monoclonal antibody fragment that binds to free dabigatran and to thrombin-bound dabigatran, which leads to neutralization of dabigatran’s activity.<sup>25</sup> While no antidotes are commercially available to reverse the anticoagulant effects of factor Xa inhibitors, the protein andexanet alfa is in the pipeline, though not yet FDA-approved. Clinical data about this potential reversal agent were presented at the 2017 American College of Cardiology’s Annual Scientific Session.<sup>26</sup> Drawbacks to NOAC therapy include higher cost; lack (so far) of data relating to efficacy and safety in those with severe chronic kidney disease; its inadvisability of use in AF patients with a mechanical heart valve; and lack of a reversal for certain drugs.<sup>2,19,24</sup> In patients who cannot afford the newer agents and when VKA is not an option, data from the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events-Aspirin (ACTIVE-A) Trial suggest that the combination of aspirin and clopidogrel is superior for stroke prevention than aspirin alone.<sup>7</sup>

## CARDIOVERSION

Pharmacologic and direct cardioversion are 2 options for patients needing rhythm control. If no contraindications are present, flecainide, dofetilide, propafenone, and intravenous ibutilide can be used to pharmacologically convert a patient back into normal sinus rhythm (class I recommendation). Amiodarone may also be used; however, it is important to note that practice guidelines do not consider this a first-line choice (class IIa recommendation).<sup>2</sup> Direct, or electrical, cardioversion is among the most effective means for converting a patient back to normal sinus rhythm.<sup>27</sup> To restore normal sinus rhythm, direct cardioversion employs an electrical current delivered by a defibrillator during the QRS complex (the Q, R, and S waves) to depolarize cardiac cells.<sup>13</sup> Success rates for this method of cardioversion range from 75% to 93%, declining to approximately 50% when AF has been present for more than 5 years. Advantages of direct cardioversion compared with pharmacological conversion include a decreased procedure duration, higher success rate, and a lower risk of proarrhythmia.<sup>27</sup> Direct-current

cardioversion is also a class I recommendation for AF patients requiring rhythm control.<sup>2</sup>

## SURGERY

Open-heart surgical ablation to treat AF was introduced in the late 1980s by James Cox, MD. His initial procedure utilized a set of complicated incisions resembling a maze on the left and right atria.<sup>28</sup> These incisions form scars that cause electrical impulses to move from the sinus node to the AV node, and prevents the formation of micro-reentry circuits that are needed to maintain AF.<sup>13</sup> While this procedure has evolved since its debut, it remains a very complex technique that few surgeons perform.

The current iteration of the Maze procedure now uses surgical ablation instead of actual incisions and is sometimes called Cox Maze IV.<sup>28</sup> The Cox Maze IV procedure, also referred to as the “cut-and-sew Maze,” is the gold standard for patients with AF needing surgical intervention to restore normal sinus rhythm.<sup>13</sup> The Maze IV procedure successfully restores both rate and rhythm while decreasing the incidence of stroke.<sup>28</sup> The surgical Maze procedure may be used in selected patients undergoing cardiac surgery for other indications (class IIa recommendation) or as a stand-alone procedure in patients with highly symptomatic AF not well managed with other treatment approaches.<sup>2</sup>

## CATHETER ABLATION

Another increasingly popular option for AF patients is catheter ablation (CA) to normalize sinus rhythm, for those who do not respond to or are not good candidates for antiarrhythmic drug therapy.<sup>29</sup> Technological advances have spurred its more frequent use. During CA, a minimally invasive procedure, a catheter is inserted into the heart via large blood vessels. Once the physician has identified where the abnormal electrical impulses are originating, radiofrequency or cryogenic energy is delivered to those tiny areas of the heart muscle to stop the irregular pulses.<sup>30,31</sup> In radiofrequency ablation, current is applied in a point-by-point fashion, leading to cellular necrosis when the tissue is heated. In ablation utilizing cryogenic energy, a balloon is utilized to deliver cryogenic energy that, in one step, freezes the tissue, causes necrosis, and stops the pulses.<sup>31</sup>

Due to its complexity, the radiofrequency approach was performed in only a few specialized US centers; however, cryoablation is a much simpler approach. The FIRE AND ICE trial was a randomized, open-label study comparing the 2 techniques in patients with paroxysmal AF. Each treatment group had more than 300 patients assigned to it, and results demonstrated that cryoablation was noninferior to radiofrequency ablation.<sup>31</sup>

Practice guidelines suggest that CA is useful as a rhythm control strategy for patients with symptomatic paroxysmal AF refractory and who may be intolerant to at least 1 class I or III antiarrhythmic drug, once benefits and risks have been evaluated (class I recommendation).<sup>2</sup> CA may be considered as a first-line therapy for patients with recurrent symptomatic paroxysmal AF for rhythm control before pharmacologic therapy is tried, after comparing risks and benefits of drug and ablation therapies (class IIa recommendation).<sup>2</sup> Despite increasing popularity

of CA for rhythm control in AF patients, the procedure does come with certain risks, including thromboembolism and hemorrhagic complications.<sup>32</sup> Before a patient undergoes CA, the clinician may choose to continue the patient's current anticoagulant therapy, or to hold their current anticoagulant and bridge the anticoagulant therapy with a low-molecular-weight heparin (LMWH). Evidence suggests that the continuation of warfarin in a patient undergoing CA is associated with decreased thromboembolic events and a lower rate of minor bleeding when compared with bridging VKA therapy with an LMWH.<sup>32</sup> Finlay and colleagues evaluated safety and cost of conversion to LMWH before catheter ablation of atrial flutter versus uninterrupted warfarin in a nonrandomized, case-control study, and determined that the uninterrupted warfarin strategy was safer and more cost-effective than periprocedural conversion with LMWH. The mean cost per patient using anticoagulation with LMWH was approximately \$150 per patient compared with \$15 per patient for uninterrupted warfarin.<sup>33</sup>

## UNINTERRUPTED ANTICOAGULATION

### VKA versus NOAC

Previous evidence has suggested that, for AF patients undergoing CA, uninterrupted anticoagulation with a VKA may be safer and more effective than bridging. However, the ActiVe-controlled multi-center study with blind adjudication designed to evaluate the safety of uninterrupted Rivaroxaban and uninterrupted VKA in subjects undergoing catheter ablation for nonvalvular Atrial Fibrillation (VENTURE-AF) trial was the first randomized trial to investigate uninterrupted anticoagulation with a VKA compared with a NOAC.<sup>34</sup> Rivaroxaban selectively inhibits factor Xa to decrease thrombin generation.<sup>35</sup> In a study of NVAf patients who were at a moderate to high risk for stroke, rivaroxaban was found to be noninferior to warfarin for the prevention of stroke or systemic embolism. There was also no significant difference in the risk of major bleeding when comparing rivaroxaban with warfarin; however, intracranial and fatal bleeding occurred less often with rivaroxaban. Rivaroxaban may be preferred in certain patients due to the lack of food-drug/drug-drug interactions associated with rivaroxaban, and due to the necessity of frequent coagulation monitoring associated with warfarin.<sup>22</sup>

VENTURE-AF was a multinational, randomized, open-label, parallel-group phase IIIb study. Researchers randomly and evenly assigned patients with planned CA to receive either an orally administered VKA, titrated to maintain an INR between 2.0 and 3.0, or an orally administered dose of rivaroxaban 20 mg daily. Inclusion criteria for the study included patients 18 years or older who had either paroxysmal, persistent, or long-standing persistent NVAf. Patients were excluded from the study if they were determined to have valvular AF, which is defined as the presence of a prosthetic heart valve (excluding annuloplasty, with or without prosthetic ring, commissurotomy, and/or valvuloplasty), hemodynamically significant mitral valve stenosis, or rheumatic heart disease. The number of patients needed to determine superiority or noninferiority between the 2 groups was determined to be too large to study; therefore, the investigators opted for a descriptive comparison by selecting the number of subjects they felt would yield clinically

relevant results. Since patients enrolled in the study were scheduled in advance to receive CA, the study design allowed for 2 pathways. Patients either followed a delayed CA pathway and were required to take anticoagulation for 3 weeks prior to the procedure, or they were placed on an advanced schedule to receive anticoagulation for as little as 1 day, and up to 7 days, prior to the procedure if diagnostic criteria demonstrated the absence of a clot within the heart. Each treatment group received intravenous unfractionated heparin (UFH) during the procedure in order to achieve a target-activated clotting time (ACT) of 300 to 400 seconds. Anticoagulation was continued post procedure for approximately 30 days, with the post study treatment regimen determined by the patient's provider. While the primary endpoint of the study was to examine the incidence of major bleeding events between the 2 treatment groups within the first  $30 \pm 5$  days post CA, major secondary endpoints were also evaluated. These included composite and individual cases of ischemic stroke, noncentral nervous system systemic embolism, MI, and vascular death, as well as other bleeding events and AEs related to the procedure. A major bleeding event was judged to have occurred by an independent clinical endpoint committee based on it meeting at least 1 of following the definitions: an International Society on Thrombosis and Haemostasis (ISTH) major bleed, a Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe/life-threatening bleed, or a Thrombolysis in Myocardial Infarction (TIMI) major bleed.<sup>34</sup>

Given that this study was exploratory in nature and not designed to determine statistical significance, the findings have limited value in determining a new standard of care. The authors of the study pointed to the combined retrospective evidence to conclude that there may be a higher complication rate with uninterrupted anticoagulation prior to CA, but stated that the results of the study should be viewed with caution. The open-label design of the study was of particular concern, as it allowed the provider to know the treatment regimen and thus introduced the potential for bias. Although limitations related to the size of the cohorts and already low numbers of observed bleeding events in patients treated by the highly skilled electrophysiologists in the study prohibit drawing definitive conclusions, the study was well designed and attempted to minimize the impact of confounders. The study employed a randomized international multicenter design coupled with blind adjudication of events in an effort to reduce reporting bias. This study adds to the growing evidence that the use of uninterrupted VKA or uninterrupted factor Xa inhibitors such as rivaroxaban may be safe, effective alternatives to bridging patients for CA procedures. However, more investigations in this area are warranted to achieve more confidence in this approach. As such, practitioners should continue to determine the best treatment strategy available utilizing their experience in practice and current treatment guidelines to develop a plan that is individualized to the patient to achieve the best outcome with minimal complications.<sup>34</sup>

A second study, RE-CIRCUIT, evaluated uninterrupted dabigatran compared with uninterrupted warfarin in patients undergoing AF ablation. This randomized, open-label, multicenter, controlled trial included patients aged  $\geq 18$  years with documented paroxysmal or persistent NVAf within the previous 24 months who were scheduled

for AF ablation and were candidates for dabigatran 150-mg twice-daily treatment. Patients with valvular or irreversible AF, or AF secondary to a reversible cause, were excluded from the study. Treatment group assignments were carried out using a 1:1 ratio. Patients received either dabigatran 150 mg twice daily or warfarin with dose adjustments to maintain a target INR, with therapeutic range defined as 2.0-3.0. A combination of warfarin 1-, 3-, and 5-mg tablets were used to adjust warfarin dosing. If a patient had been treated with a VKA before the study, study treatment was not initiated until the individual's INR was below 3 (for warfarin) or below 2 (for dabigatran). This study utilized 4 different treatment phases: 1) 0-2 weeks of screening; 2) 4-8 weeks of anticoagulation before ablation to ensure goal anticoagulation range was achieved; 3) 8 weeks of post CA anticoagulation; and 4) 1 week of follow-up.<sup>36</sup>

To rule out the presence of a thrombus in the left atrium prior to CA, all patients underwent transesophageal echocardiography prior to the procedure. Patients in the dabigatran group were given the morning dose of the regimen prior to the ablation and the evening dose timed to occur at least 3 hours after sheath removal and after the achievement of hemostasis. As described in the VENTURE-AF study, all patients were given UFH during the procedure to maintain the goal ACT of  $>300$  seconds. While radiofrequency was the primary technique used in this study, other modalities were allowed, including cryoablation and laser ablation. Ablation was performed as determined by the attending electrophysiologist and according to recommendations and guidelines based on the 2012 expert consensus statement. Several safety and efficacy endpoints were evaluated in this study; however, the primary endpoint was incidence of adjudicated ISTH major bleeding events. Events occurring from the start of the ablation procedure up to 8 weeks post ablation were included in the analysis. Secondary endpoints for this study included incidence of a composite of stroke; systemic embolism or transient ischemic attack (TIA); minor bleeding events; and bleeding events combined with thromboembolic events (stroke, systemic embolism or TIA). In order to have enough power to determine statistical significance for noninferiority, each treatment group would have needed more than 2000 patients. Since the researchers thought this was unfeasible, an exploratory approach was used similar to that of the VENTURE-AF trial, and it was determined that clinically meaningful data could be provided if a goal of 290 patients per treatment group was met. A total of 317 patients were randomized to the dabigatran group and 318 to the warfarin group. Both demographic and clinical characteristics were similar among treatment groups. Most patients enrolled in the study were diagnosed with paroxysmal AF. The mean age of patients included in the study was 59 years and patients were predominately men (73%).<sup>36</sup> Adherence rates for patients receiving dabigatran was determined by calculating the number of pills taken. Patients who had not met 80% to 120% of the anticipated dose were considered nonadherent. The mean adherence rate for patients taking dabigatran was 97.6%. To determine adherence in the warfarin group, a therapeutic INR goal of 2.0-3.0 was used. Patients in the INR-adjusted warfarin group were within goal INR range 66% of the time. A total of 86% of dabigatran patients and 84% of warfarin patients received trial medication for at least 8 weeks post ablation, and more than 98% of

trial participants received medication for at least 6 weeks. Incidence of major bleeding events, the primary endpoint of the study, was observed in 1.6% of patients in the dabigatran group and 6.9% of patients in the warfarin group (95% CI, -8.4 to -2.2;  $P < .001$ ). Cox proportional-hazards analysis demonstrated a hazard ratio of 0.22 (95% CI, 0.08-0.59) for dabigatran compared with warfarin.<sup>36</sup>

Use of anticoagulation of any mechanism is associated with a risk of bleeding. Events of pericardial tamponade, groin hematoma, intracranial bleeding, gastrointestinal bleeding, pseudoaneurysm, and hematoma were observed less frequently in the dabigatran group than in the warfarin group. There were 4 major bleeding events in the dabigatran group within 7 days post ablation, compared with 17 events in the warfarin group. Comparing patients in the warfarin group with and without major bleeding events, the mean INR was similar (2.4 vs 2.3).<sup>36</sup>

Secondary outcomes in this study included incidence of stroke, systemic embolism, or TIA, and the rate of serious AEs. A serious AE in patients who had taken at least 1 dose of the study drug occurred in 22.2% of the warfarin group and 18.6% of the dabigatran group. Severe events were observed in 3.3% of dabigatran patients versus 6.2% of warfarin patients.<sup>36</sup>

In addition to bleeding risks, stroke is a potential complication in patients undergoing CA. No reports of stroke or TIA were reported in the dabigatran group and only 1 TIA occurred in the warfarin group. The composite of major bleeding and thromboembolic events was 1.6% in the dabigatran group versus 7.2% in the warfarin group.<sup>36</sup>

Analysis of the results indicates significantly lower rates of major bleeding events in the dabigatran group. Of particular note were fewer incidents of groin hematoma and life-threatening bleeds such as pericardial tamponade. Researchers postulated that the observed differences in bleeding events might be related to 2 specific factors. First, they referenced the shorter half-life of dabigatran versus treatment with a VKA, which has a much longer half-life. Secondly, the authors pointed out that dabigatran's mechanism of action through direct thrombin inhibition preserves factor VII levels, whereas VKA exhibits a broad-spectrum anticoagulation by impacting several coagulation factors, including factor VII. As in the VENTURE-AF trial, the RE-CIRCUIT trial lacks statistical power due to the small sample size as well as the open-label design.<sup>36</sup>

The authors noted a recent meta-analysis, involving 7996 patients from 19 observational studies, that supports the use of an uninterrupted NOAC as a viable treatment strategy to prevent thromboembolic events in patients undergoing CA. The study indicated that NOACs may be associated with a lower rate of bleeding complications.<sup>36</sup> Results from the RE-LY trial, which demonstrated an advantage of dabigatran over VKA, add to the growing evidence of the safety and efficacy of utilizing NOACs in patients with AF.<sup>36</sup>

## MANAGED CARE IMPLICATIONS

Evidence suggests that AF cost-reduction strategies can be effective by shifting cost from inpatient to outpatient care. Utilization of treatment algorithms in the emergency department have been shown to be effective in avoiding hospital admission and allowing for follow-up in

AF clinics in the outpatient setting to reduce costs. When developing algorithms, it is important to note that evidence suggests rate control is a more cost-effective approach than rhythm control. Additionally, improving utilization, management, and adherence to anticoagulation therapy has been shown in numerous studies to improve outcomes and should be part of focused efforts in this heavily "at risk" population.<sup>7</sup>

Over the last 15 years, CA has evolved and emerged as the primary treatment option available for rhythm control.<sup>4</sup> With older literature references demonstrating success rates that varied widely, recent studies suggest that success rates of >80% can be achieved in patients with paroxysmal AF.<sup>7</sup> However, it has been difficult to demonstrate AF as a cost-effective strategy in all cases due to the inherent difficulties in study comparisons and the subsequent ability to generalize results.<sup>4,7</sup> Utilization of different technologies (radiofrequency ablation vs cryoablation), different measurements of success, and a general lack of understanding of the long-term effects of CA on cost and outcomes in patients with AF, all contribute to the need for further study.<sup>4</sup>

Chang et al performed a literature review on the cost-effectiveness of CA; all studies they reviewed used a modeling-based approach to extrapolate the impact of CA. They noted that existing randomized controlled trials for CA in AF have failed to report long-term cost and quality-of-life (QOL) results.<sup>4</sup> In the cost-effectiveness analysis studies, Chang et al found that several input assumptions made by the authors of the individual studies could substantially change the results and must be confirmed (or challenged) with further research. To achieve greater modeling accuracy, Chang et al suggested that more needs to be known about CA, including long-term outcomes and costs. They outlined a framework for further study that includes measuring effect on QOL, calculating ability to maintain normal sinus rhythm, and tabulating readmissions associated with recurrent AF, as well as quantifying the interrelationship among CA and HF, stroke, and mortality. Variability in these factors can push the incremental cost-effectiveness ratio calculation beyond the "willingness-to-pay" threshold of \$100,000 per quality-adjusted life-year.<sup>4</sup>

Given the current literature available, evidence suggests that CA may achieve the most benefit in younger patients with symptomatic disease, especially those who fail antiarrhythmic drug treatment. Further study would be needed to justify the use of CA in all cases, across the board, given the facts that complications related to the procedure can certainly outweigh its benefits, and that lower-cost alternatives, such as pharmacologic rate control, are better understood. Advances in technology may also improve outcomes, as well as lower the costs and decrease the risks associated with CA.<sup>4</sup>

While there are other methods of CA not mentioned here, it is certain that reducing thromboembolic complications using safe and effective uninterrupted anticoagulation is of prime importance. Until recently, standard of care has been to stop VKA therapy and bridge patients with LMWH prior to and after CA. However, as previously mentioned, studies have shown that this may not be the safest, nor the most effective, strategy.

Evidence appears to favor the utilization of uninterrupted anticoagulation utilizing either a VKA or an NOAC, such as dabigatran or rivaroxaban, prior to and post CA.<sup>33</sup>

By reducing thromboembolic complications and minimizing bleeding events, overall costs of care would be reduced. Given the rising healthcare costs attributed to AF, any incremental reduction in costs benefits not only the patient, but the entire healthcare system.

Given the small sample sizes and lack of statistically powered results, managed care providers should be cautious not to overgeneralize the results of these studies. However, given that bridging patients on NOACs or with a VKA is a practice existing today, and new data to support this practice are available, there does appear to be an opportunity to reduce the direct costs associated with the more traditional strategy of bridging VKA patients with LMWH. Certainly, reviewing internal quality metrics related to CA, and reviewing outcomes and complications, should help to drive medical policy. It should be a reasonable goal to develop treatment algorithms, with the input of cardiovascular specialists who perform CA, without relying on older, less effective practices that lead to more complications, yet ensuring that patients enjoy uninterrupted anticoagulation prior to and post CA. Collecting data and reviewing outcomes using uninterrupted VKA and newer NOACs should help to further drive practice changes. And although a reversal agent was available during the time of the RE-CIRCUIT trial, major bleeding events were managed without the need to use the drug. Under study conditions, it would be expected that the goal would be to minimize the use of reversal agents; however, in a real-world practice setting, the inappropriate use of expensive reversal agents has the potential to drive up costs and should be monitored closely. From a managed care perspective, identifying centers of excellence that perform these procedures with the fewest complications and the most effective outcomes, and that are reproducible at the lowest cost, should help to drive medical policy and population management. •

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