EXPERT REVIEWS

Atrial fibrillation: an epidemic in the elderly

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Anne B Riley[1] and Warren J Manning[†1]

[1]*Beth Israel Deaconess Medical Center, Department of Cardiology, Boston, MA, USA*
[†]*Author for correspondence: Tel.: +1 617 975 5480 wmanning@bidmc.harvard.edu*

Atrial fibrillation is the most common cardiac arrhythmia that increases in prevalence with age. As the general population grows older, general practitioners will more frequently see this disease in their clinic population. In order to most effectively treat these patients, physicians need to understand key issues, including the use of rhythm control versus ventricular rate control and how to reduce the risk of ischemic stroke. This article will review recent advancements in the understanding of the pathophysiology, management, stroke risk stratification and prevention of thromboembolic complications in atrial fibrillation.

Keywords: atrial fibrillation • cardioversion • CHADS2 • CHA2DS2-VASc • dabigatran • dronedarone • pulmonary vein isolation • rhythm control • transesophageal echocardiogram • ventricular rate control

Epidemiology

Atrial fibrillation (AF) is the most common sustained arrhythmia, affecting over 2 million Americans [101]. Census-based projections show there will be over 7 million Americans with AF by the year 2050 [1]. The lifetime risk for developing AF is estimated to be one in four for both men and women at 40 years of age and older [2]. AF becomes much more prevalent as the population ages, with a prevalence of 0.1% in individuals younger than 55 years, 3.8% among those 60 years and older, and 9% in those 80 years and older [3].

Atrial fibrillation is associated with substantial morbidity and mortality. It increases the risk of stroke by three- to five-fold, creating a huge burden on our medical system and a negative impact on individual patients' lives [4]. The risk of stroke attributed to AF also increases with age, from 1.5% at age 50–59 years to 23.5% at age 80–89 years [4]. AF also independently increases the risk of congestive heart failure and the risk of death by 1.5–2-times compared with patients in sinus rhythm [5,6]. Finally, AF appears to increase the incidence of dementia in patients with a history of stroke [7].

Risk factors associated with the development of AF include diabetes (odds ratio [OR]: 1.4 for men and 1.6 for women), hypertension (OR: 1.5 for men and 1.4 for women), congestive heart failure (OR: 4.5 for men and 5.9 for women) and valvular heart disease (OR: 1.8 for men and 3.4 for women) [8]. Diastolic dysfunction is independently associated with the development of AF [9]. Coronary artery disease, obstructive sleep apnea, hyperthyroidism and cardiac surgery have all been associated with the development of AF, as well as heavy alcohol use [10]. Primary care providers, particularly those who care for elderly individuals, will see this disease frequently among their clinical population.

Pathophysiology

The development and continuance of AF is a complex and debated field. Numerous factors appear to influence the initiation or 'trigger' and others contribute to a cardiac substrate that allows the continuance and propagation of AF. Ectopic beats have been shown to have a causal role in the initiation of paroxysmal AF. Most of these beats come from the foci within the pulmonary veins [11], with the left superior pulmonary vein being the most common initiation site. Less commonly, ectopic foci are found in the right or left atrium and infrequently found in the superior vena cava [11]. This information has led to the development of interventional electrophysiologic techniques to try and isolate these ectopic foci (see rhythm control section). More recently, remodeling of both the atrial electrical system and the structural properties of the atria have been shown to be closely associated with a substrate that allows for the continuance of AF. Electrical remodeling is primarily due to the effects of a sustained high atrial rate and results in a shortening of the refractory time of atrial myocytes. In animal models, electrical

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remodeling can then sustain AF [12]. Structural remodeling has become the focus of many recent studies [13,14]. Atrial fibrosis occurs as the result of the accumulation of collagen deposits in AF patients [15]. The cause–effect relationship between AF and atrial fibrosis has not been well established, but there likely exists a circular feedback mechanism by which one begets the other.

Treatment

Rate control

Providers are faced with the decision to either adopt a ventricular rate control or rhythm control strategy for patients with AF. There are a number of hallmark studies that have compared the two approaches. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial, published in 2002, enrolled 4060 patients (mean age: 69.7 years) with recurrent AF and assigned them to a ventricular rate control strategy (using β-blockers, calcium channel blockers and/or digoxin) versus a rhythm control strategy (using antiarrhythmic medications) [16]. Chronic anticoagulation was required only in the ventricular rate control arm. In the rhythm control arm, anticoagulation was required until the patient maintained sinus rhythm, at which point anticoagulation could be withdrawn at the discretion of the provider. Patients were followed for a mean of 3.5 years. Patients in the ventricular rate control group showed a trend towards decreased all-cause mortality, the primary end point. A follow-up study showed that the trend towards increased mortality in the rhythm control group was caused by adverse effects of antiarrhythmic drugs [17]. The rates of the composite end point of death, disabling stroke, disabling anoxic encephalopathy, major bleeding or cardiac arrest were similar in the two groups. The rhythm control strategy was associated with a significantly higher risk of death in a few prespecified subgroups, which included those aged over 65 years, those without congestive heart failure and those with coronary artery disease. The results of this study showed that the ventricular rate control strategy is as effective as rhythm control and may pose a reduced risk compared with rhythm control. Of note, ischemic strokes occurred predominantly in patients whose warfarin had been discontinued or in whom the international normalized ratio (INR) was subtherapeutic (INR < 2), regardless of their assignment to rhythm or ventricular rate control strategies. This study provides support for the concept that patients are still at equivalent risk for stroke no matter which strategy (rate vs rhythm control) is chosen and that warfarin anticoagulation is beneficial to prevent stroke independent of rhythm.

The second major trial comparing the two strategies, the Rate Control Versus Electrical Cardioversion For Persistent Atrial Fibrillation (RACE) trial, was also published in 2002 [18]. In this study, 522 patients (mean age: 68 years) with persistent AF who had already undergone cardioversion were assigned to either a ventricular rate control or rhythm control strategy. The ventricular rate control strategy used the same medication options as in the AFFIRM trial and required that all patients older than 65 years as well as those younger than 65 years but with underlying cardiac disease be treated with chronic warfarin anticoagulation. The rhythm control strategy consisted of serial cardioversions and a protocol of antiarrhythmic medications, which included trials of sotalol, propafenone, flecainide and amiodarone. Patients were required to be anticoagulated for 4 weeks before continuing until 4 weeks after each cardioversion. If sinus rhythm persisted for 1 month, anticoagulation could be stopped. Patients were followed for a mean of 2.3 years. The primary end point was a composite of death from cardiovascular causes, heart failure, thromboembolic complications, bleeding, implantation of a pacemaker and severe adverse effects of drugs. The RACE trial also demonstrated a trend towards reduction of the primary end point with ventricular rate control. The rate of cardiovascular mortality was similar, but there was a trend towards a higher incidence of heart failure, thromboembolism, pacemaker insertion and adverse drug reaction in patients assigned to the rhythm control group. Thromboembolic events also occurred more frequently in the rhythm control group than the rate control group. As with the AFFIRM trial, most occurred in the setting of either no anticoagulation therapy or with a subtherapeutic INR.

As a result of these studies ventricular rate control is now often considered first-line therapy in patients with AF. The question of what the goal heart rate should be has largely been an empiric decision left to individual providers. The investigators in the AFFIRM study set goals of a resting ventricular rate of no more than 80 bpm and a rate of no more than 110 bpm during a 6-min walk test. In the RACE study, the investigators set a goal of less than 100 bpm and no symptoms. More recently, the RACE II trial sought to answer the question of whether lenient rate control in AF is equivalent to strict rate control [19]. Investigators assigned 614 patients (mean age: 68 years) with permanent AF to a lenient rate control strategy (resting heart rate of less than 110 bpm) or a strict rate control strategy (resting heart rate of less than 80 bpm and a heart rate during moderate exercise of less than 110 bpm). The primary outcome was a composite of death from cardiovascular causes, hospitalization for heart failure, stroke, systemic embolism, bleeding and life-threatening arrhythmic events. The mean resting heart rate in the lenient group was 93 bpm compared with 76 bpm in the strict control group ($p < 0.001$). After 2–3 years of follow-up, the lenient rate control strategy was found to be noninferior to the strict control strategy. There was no difference in patient-reported symptoms of palpitations, dyspnea and fatigue at the end of the follow-up period. Issues with the study results include a short follow-up period. Providers cannot be certain what affect high ventricular rates will have on the cardiovascular system over years to decades. However, this study does open the door to questions about the appropriateness of a strict ventricular rate control strategy.

Rhythm control

Due to the results of the RACE and AFFIRM studies, rate control has emerged as a preferred strategy for the majority of patients with AF, particularly if the AF is recurrent and the patient is asymptomatic. We know from the aforementioned studies that rhythm control does not negate the need for chronic anticoagulation, so patients with rhythm control will not have the advantage of coming off their oral anticoagulant. However, certain situations may invoke reasons

to proceed with a rhythm control strategy. For example, some patients may have persistent symptoms attributable to AF, including fatigue, dyspnea and palpitations, despite optimal rate control. These patients may warrant a trial of rhythm control. In addition, patients who cannot be adequately rate controlled or patients with persistent heart failure may benefit from a rhythm control strategy. Finally, some patients simply may prefer a rhythm control strategy.

There are a number of antiarrhythmic therapies, both medical and surgical, that can help patients maintain sinus rhythm. The medical options should be tailored to each individual patient's underlying clinical condition. The American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/ Heart Rhythm Society (HRS) provides guidelines to help clinicians choose between the various antiarrhythmic drug therapies (Figure 1A–D) [20]. Patients without any underlying structural heart disease may be appropriate candidates for treatment with flecainide, propafenone, dronedarone or sotalol. These agents may be used in patients with hypertension if left ventricular hypertrophy is not present. Amiodarone or dofetilide are considered second-line therapy. For patients with heart failure or a left ventricular ejection fraction no more than 35%, amiodarone or dofetilide are the recommended initial agents of choice. For patients with coronary artery disease, dronedarone, dofetilide or sotalol are the preferred options. Amiodarone may also be used. Flecainide and propafenone should be avoided in patients with coronary artery disease. The Cardiac Arrhythmia Suppression Trial (CAST) found that patients with nonsustained ventricular tachycardia after myocardial infarction who were prescribed flecainide had an increased mortality [21]. Similar recommendations are followed for propafenone, although it was not included in CAST.

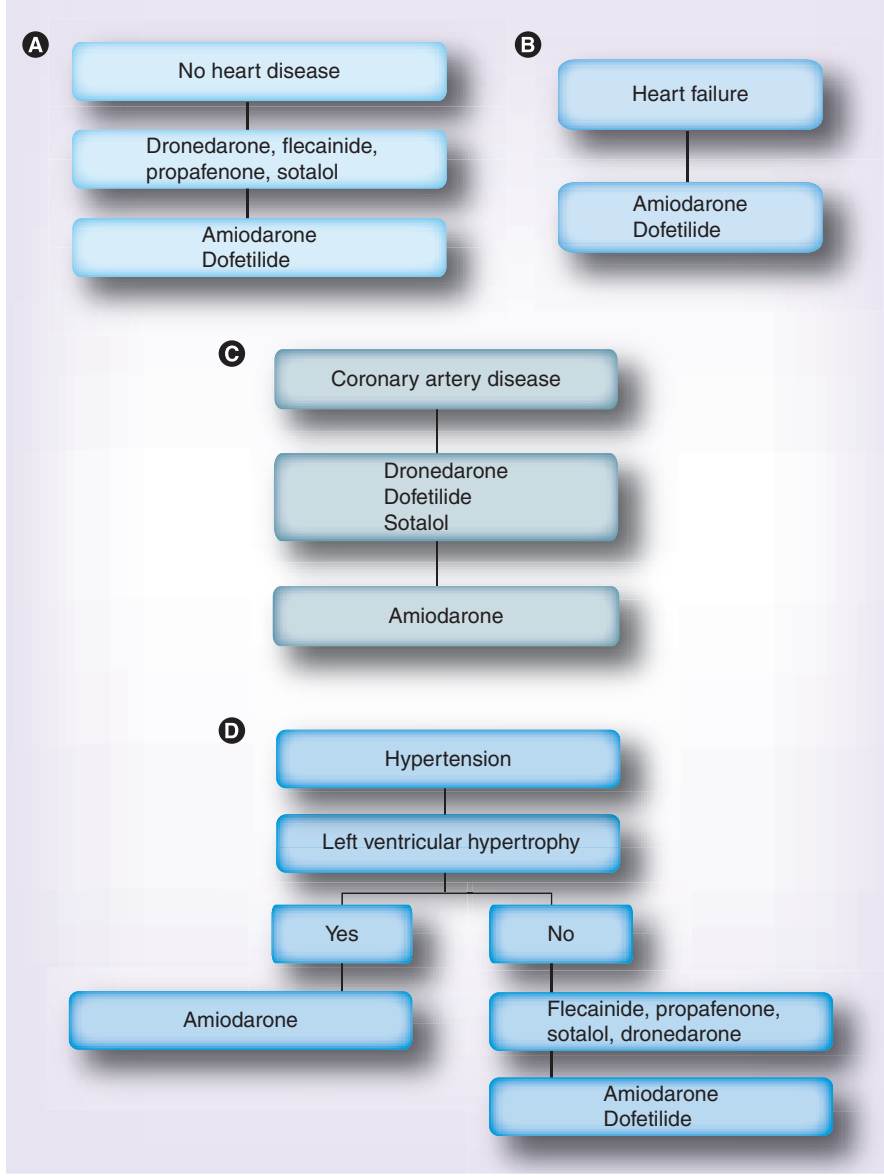

Figure 1. Antiarrhythmic management of atrial fibrillation. (A) Guidelines for antiarrhythmic medication use in atrial fibrillation (AF) in patients with no or minimal heart disease. **(B)** Guidelines for antiarrhythmic medication use in AF in patients with heart failure. **(C)** Guidelines for antiarrhythmic medication use in AF in patients with coronary artery disease. **(D)** Guidelines for antiarrhythmic medication use in AF in patients with hypertension.
Adapted from [20].

Each of these antiarrhythmic agents has a side-effect profile and efficacy rate that should be considered prior to initiation of therapy in any individual patient. In particular, all antiarrhythmic medications have proarrhythmic activity, the most feared of which is ventricular tachycardia and torsades de pointes. In maintenance of sinus rhythm, propafenone was found to induce ventricular arrhythmias in up to 3% of patients, sotalol in up to 5% of patients and quinidine in up to 12% of patients [22]. Flecainide, disopyramide and amiodarone did not appear to cause any reported ventricular arrhythmias. Amiodarone has a lower risk of promoting ventricular arrhythmias, but has significant noncardiac toxicities that include thyroid disease, lung disease (both acute and chronic), hepatic dysfunction, skin toxicity and neurologic abnormalities that often cause its discontinuation [23]. Frequent monitoring is therefore required. The American College of Physicians and the American Academy of Physicians have published a review of the clinical trials outlining the efficacy of individual antiarrhythmic agents [22]. They found 'strong evidence' of efficacy for amiodarone, propafenone, disopyramide and sotalol,

with amiodarone showing the most success in maintaining sinus rhythm. They found 'moderate evidence' for flecainide, quinidine and azimilide [22].

Dronedarone is a new antiarrhythmic agent that was approved for use in the USA in 2009. It is a noniodinated amiodarone congener, with alterations made in chemical composition in an effort to reduce the side effects seen with amiodarone. Two major trials have evaluated its effectiveness in maintaining sinus rhythm in patients with paroxysmal or persistent AF. The European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) trial and the American–Austrialian–African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) trial [24] collectively randomized 1237 patients to dronedarone or placebo. The AF recurrence rate at 12 months was significantly lower in the dronedarone group (64.1%) versus the placebo group (75.2%; $p < 0.001$). The Antiarrhythmic Trial With Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) trial examined the use of dronedarone in patients hospitalized with symptomatic heart failure, regardless of a history of AF [25]. Patients with New York Heart Association class III or IV heart failure and left ventricular ejection fractions of less than 35% were randomized to receive dronedarone or placebo. The trial was prematurely stopped secondary to an excess of deaths in the dronedarone group (8.1% of patients) versus the placebo group (3.8% of patients; $p = 0.03$). Dronedarone has also been compared directly with amiodarone to assess its efficacy and side-effect profile. The Efficacy and Safety of Dronedarone versus Amiodarone for the Maintenance of Sinus Rhythm in Patients with AF (DIONYSOS) trial randomized 504 patients with persistent AF to dronedarone or amiodarone [26]. The primary outcome was a composite end point of recurrent AF (with ECG documentation) or study drug discontinuation for intolerance. A main safety end point (MSE) included predefined thyroid, hepatic, pulmonary, neurological, skin, ocular and gastrointestinal adverse events, or premature study drug discontinuation. At 12 months, 75.1% of patients on dronedarone and 58.8% of patients on amiodarone had reached the primary end point ($p < 0.001$). This difference was largely driven by higher AF recurrence with dronedarone compared with amiodarone (63.5 vs 42.0%). However, dronedarone had a lower incident of the MSE compared with amiodarone (39.3 vs 44.5%, respectively; $p = 0.129$). This difference was reflective of fewer thyroid, neurologic, skin and ocular events in the dronedarone group. In this study, dronedarone had a safer side-effect profile compared with amiodarone, but was not as effective as amiodarone in maintaining sinus rhythm. Of note, in early 2011, the US FDA put forward a report of several case reports of hepatocellular liver injury and hepatic failure in patients treated with dronedarone, including two postmarketing reports of acute hepatic failure requiring transplantation. The FDA recommends that providers advise patients to contact a healthcare professional if they experience anorexia, nausea, vomiting, right upper quadrant pain or other signs of liver injury. They also recommend that healthcare professionals consider checking liver enzymes periodically in patients taking dronedarone, especially during the first 6 months of therapy. In this safety alert, the FDA also emphasizes their recommendation that dronedarone should not be used in patients with severe heart failure [102]. In addition, the FDA has recently announced concerns regarding the use of dronedarone for treatment in patients with permanent AF [103]. Based on their review of data from the Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS), there was a significant excess of cardiovascular events in the dronedarone group for both coprimary end points (cardiovascular death/myocardial infarction/stroke/systemic emboslim; death/unplanned cardiovascular hospitalization) as well as other cardiovascular events. As a result, the PALLAS study was prematurely stopped.

Radiofrequency catheter ablation can be used in selective patients to reduce and/or eliminate recurrence of AF. The rationale for radiofrequency catheter ablation originates with the understanding that AF is often triggered by ectopic beats originating in the pulmonary veins [11]. The most commonly used radiofrequency technique uses a catheter-delivered electrical current to create a ring around each pulmonary vein as it enters the left atrium [27]. By electrically isolating the pulmonary veins, the ectopic beats cannot disseminate to the left and right atria and a trigger for AF is theoretically eliminated. There is an overall complication rate of 4.5%, including 1.3% risk of tamponade, 0.9% risk of stroke or transient ischemic attack (TIA), less than 1% risk of pulmonary stenosis, a 0.04% risk of atrioesophageal fistula and a 0.15% risk of procedural death [28]. Tan *et al.* examined the efficacy of catheter ablation in octogenarians compared with younger patients and found that success rates were similar between the groups at a mean follow-up of 18 months [29]. The long-term results from pulmonary vein isolation (PVI) procedures were recently presented in two separate studies. Ouyang *et al.* followed 161 patients with symptomatic paroxysmal AF and normal left ventricular function after circumpherential PVI. After a medial follow-up of 4.8 years, 53% of patients demonstrated recurrent atrial tachycardias, lasting over 30 s on electrocardiogram or Holter monitoring. The majority of recurrences occurred within the first month (41.9%) [30]. Weerasooriya *et al.* prospectively followed a total of 100 patients after their first PVI for 5 years. Arrhythmia-free survival rates after a single catheter ablation procedure were 40% at 1 year, 37% at 2 years and 29% at 5 years. Patients with long-standing persistent AF had a higher recurrence rate than patients with paroxysmal or persistent AF. Most recurrences occurred over the first 6 months and many patients had repeat procedures. Arrhythmia-free survival following the last catheter ablation (mean of two per patient) was 63% at 5 years [31]. Despite the relatively low success rate of single PVI, there is likely a particular patient population that will benefit from this procedure. The European Society of Cardiology guidelines suggest that ablation should be generally reserved for patients

with severely symptomatic AF who have failed rate control and rhythm control. However, ablation may be considered as a first-line technique in certain patients with symptomatic AF [32]. Patient characteristics that may favor higher success with PVI include patients with paroxysmal or persistent AF, smaller left atrial size and younger patients [33].

Stroke prevention

Ischemic stroke is the most dreaded complication of AF, which increases in incidence as patients increase in age (see previously). Reduction of stroke risk is therefore a critically important aspect of the management of patients with AF. Patients with valvular AF (e.g., rheumatic mitral stenosis) are at very high risk of stroke and therefore should be treated with warfarin (INR 2–3). Of note, patients with nonvalvular paroxysmal, persistent and permanent AF appear to be at similar stroke risk and should be considered the same when assessing stroke risk [34]. The first step in addressing stroke prevention is to estimate an individual patient's stroke risk. With this information, one can then decide with the patient whether anticoagulation, antiplatelet or no therapy is most appropriate. There are numerous strategies for estimating stroke risk in individuals with nonrheumatic, nonvalvular AF. Some of these include a patient's clinical features, while others also include transthoracic echocardiographic variables [35]. The CHADS2 scoring schema [36], which came out of the National Registry of AF as a combination of the Stroke Prevention in Atrial Fibrillation (SPAF) and the Atrial Fibrillation Investigators (AFI) classification schemes, is the most commonly used clinical risk stratification system. Particularly helpful is its ease of use, as it incorporates five easily assessable clinical risk features. CHADS2 is calculated by adding one point for any of the following:

- Recent congestive heart failure exacerbation (within the past 100 days);
- History of hypertension;
- Age 75 years or older;
- Diabetes mellitus.

Two points are added for history of prior stroke or neurologic event. Patients with CHADS2 scores of 0 have an adjusted stroke rate of 1.9% per year, those with a CHADS2 score of 1 have an adjusted stroke rate of 2.8% per year and those with a CHADS2 score of 2 have an adjusted stroke rate of 4% per year (Table 1). In the CHADS2-revised scoring system, patients are considered low risk if they have zero points (aspirin), intermediate risk if they have 1 point (aspirin or warfarin) and high risk if they have 2 or more points (warfarin preferred) [37]. How this risk translates into anticoagulation/antiplatelet strategies will be discussed later.

A modified CHADS2 schema for evaluating a patient's stroke risk was recently published that attempts to further refine the CHADS2 risk score, it is known as the CHA2DS2-VASc risk score [38]. CHA2DS2-VASc is similar to CHADS2 and is calculated by assigning 2 points each for age greater than or equal to 75 years and stroke/TIA/thromboembolic event and 1 point each for congestive heart failure/left ventricle (LV) dysfunction, hypertension or diabetes mellitus, as well as one point for vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque), age 65–74 years and sex (female gender). Patients with 0 points are classified as low risk (aspirin). Patients with 1 point are classified as intermediate risk (aspirin or warfarin) and patients with 2 or more points are classified as high risk (warfarin preferred). The authors propose that this new schema further refines risk stratification in AF, moving more patients out of the intermediate category and into the high-risk category [38]. A recent observational study suggests that the CHA2DS2-VASc score better characterizes patients at truly low risk and truly high risk of embolic events [39]. It remains to be seen if the addition of these risk factors can help better define which anticoagulation/antiplatelet strategy should be used in clinical practice.

Table 1. Stroke risk in nonvalvular atrial fibrillation without anticoagulation by CHADS2 score.

CHADS2 score	Adjusted stroke rate (%/year; 95% CI)
0	1.9 (1.2–3.0)
1	2.8 (2.0–3.8)
2	4.0 (3.1–5.1)
3	5.9 (4.6–7.3)
4	8.5 (6.3–11.1)
5	12.5 (8.2–17.5)
6	18.2 (10.5–27.4)

Adapted from [58].

After evaluating a patient's risk for stroke, the physician must decide between various medical strategies to try and reduce stroke risk. The basic options include anticoagulation with vitamin K antagonists (e.g., warfarin), aspirin and no therapy. Multiple studies have shown that adjusted-dose warfarin (target INR of 2–3) significantly reduces clinical stroke risk compared with aspirin or placebo in both men and women in all age categories [40]. However, the major safety concern in using warfarin is the major bleeding risk (bleeding that requires hospitalization, transfusion or surgery). Intracranial bleeding is of particular concern in the elderly population. The Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study attempted to evaluate the net clinical benefit (NCB) of anticoagulation with warfarin in a population stratified using the CHADS2 risk score [41]. NCB was defined as the difference between the annualized rate of thromboembolic events prevented by warfarin minus the annualized rate of intracranial hemorrhage induced by warfarin (weighted 1.5-times the impact of ischemic stroke). The NCB was statistically significant at a CHADS2 score of 2 and increased as the CHADS2 score increased. Even though patients with a higher CHADS2 score have a higher risk of major hemorrhage [42], they have a greater benefit from stroke reduction compared with the risk of intracranial hemorrhage/major hemorrhage [40]. The elderly population faces certain challenges with the use of warfarin, which include greater sensitivity to the drug [43], putting them at risk for increased INR levels. Elderly patients are also more likely

to be on multiple medications for various medical conditions, which may interact with and affect their INR. It is extremely important to counsel patients repeatedly about the effect that other medications may have on their INR. For example, concurrent use of nonsteroidal anti-inflammatories or antiplatelet agents including aspirin and clopidogrel in addition to warfarin will place patients at higher risk of bleeding. Physicians are also rightly concerned about an elderly patient's risk of falling while on anticoagulation. However, the fear of falls and subsequent subdural hematomas is often overstated and may cause an underutilization of warfarin in elderly AF patients [44]. Investigators at the University of Ottawa (ON, Canada) created a Markov decision analytic model to determine the preferred treatment strategy for patients with AF who are 65 years and older, are at risk for falling and are without any other contraindication to anticoagulation therapy [45]. Given the risk of subdural hematoma compared with the risk of stroke without anticoagulation, they estimated that an individual would have to fall about 295 times in 1 year for the risk of subdural hematoma to outweigh the benefits of warfarin.

Aspirin is another option to be considered in the reduction of stroke risk. However, a large meta-analysis of six major clinical trials showed that, overall, aspirin is consistently less effective than warfarin in preventing ischemic stroke [40]. That advantage was not offset by an increase in major bleeding events. For example, treating 1000 AF patients with warfarin rather than aspirin for 1 year will prevent 23 ischemic strokes but cause nine additional major bleeding episodes [40]. In addition, the Birmingham Atrial Fibrillation Treatment of the Aged (BAFTA) study examined the risks and benefits of treating patients over the age of 75 years with AF with aspirin versus warfarin. Patients over the age of 75 years were randomly assigned to receive either aspirin or warfarin. The primary end point was fatal or disabling stroke (ischemic or hemorrhagic), intracranial hemorrhage or clinically significant arterial embolism. The authors found that patients assigned to the aspirin group had significantly more events than those assigned to the warfarin group. There was not a significant difference in extracranial hemorrhage between the two groups [46]. Patients usually are more fearful of stroke as compared with major bleeding, which usually requires shorter-term treatment with transfusion and/or surgery. As stated previously, the higher the risk of embolic stroke, the greater the absolute stroke reduction with warfarin. However, aspirin has been found to be more effective in preventing stroke in AF compared with placebo [47]. There is no solid evidence to recommend one dose of aspirin over another for the reduction of stroke in AF, although 325 mg is a dose used in several clinical trials [47]. Doses ranging from 75 to 325 mg daily are reasonable. In patients with an intermediate risk of stroke (CHADS2 score of 1), there is inconclusive clinical evidence to definitively recommend anticoagulation for all patients. It is reasonable to consider whether oral anticoagulation therapy or aspirin should be used in this population [37]. Factors an individual practitioner should consider include patient risk of bleeding, ability to monitor INR and patient preference (after education regarding the risks and benefits of anticoagulation versus aspirin).

Dabigatran is a novel oral direct thrombin inhibitor that was approved in October 2010 by the FDA for prevention of embolic events in patients with AF. The major clinical trial supporting this approval, the Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) trial [48], compared dabigatran 110 mg twice daily, dabigatran 150 mg twice daily and warfarin (INR 2–3) with a primary end point of stroke or systemic embolism. The average CHADS2 score of the study patients was 2.1. Exclusion criteria included severe valvular heart disease, active liver disease, renal dysfunction with a creatinine clearance of less than 30 ml/min, pregnant women, stroke within 14 days or severe stroke within 6 months, and conditions that increased the risk of hemorrhage. Dabigatran 110 mg twice daily was associated with similar rates of stroke and systemic embolization, but a significantly reduced bleeding risk compared with warfarin. Dabigatran 150 mg twice daily was associated with significantly lower rates of stroke and systemic embolization and equal rates of major hemorrhage [48]. Dabigatran does not require monitoring of the INR, does not have warfarin's narrow therapeutic window and may have fewer drug interactions than warfarin. This may be particularly useful in the elderly population, who often have a long list of coexisting medications and may have problems monitoring their INR. Disadvantages include limited long-term follow-up data, twice-daily dosing, high

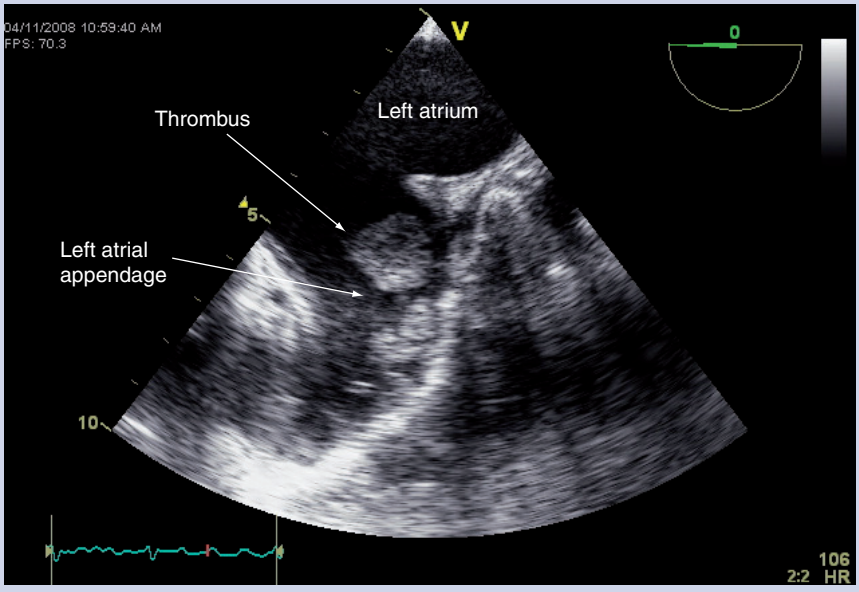

Figure 2. Left atrial appendage clot seen on transesophageal echocardiogram.

cost, potential dose adjustment required for patients with moderate-to-severe chronic kidney disease and lack of a 'reversing' agent. The FDA approved the 150-mg twice-daily dose studied by the RE-LY trial and a 75-mg twice-daily dose (not studied) for patients with an estimated glomerular filtration rate of 15–30 ml/min. Based on the results of this trial, the ACCF/AHA/HRF issued a recommendation in 2011 that dabigatran may be used as an alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with paroxysmal-to-permanent AF and risk factors for stroke or systemic embolization who do not have a prosthetic heart valve or hemodynamically significant valve disease, severe renal failure (creatinine clearance <15 ml/min) or advanced liver disease (impaired baseline clotting function) [49].

Anticoagulation for AF is particularly important to consider in the setting of electric or pharmacologic cardioversion. Patients with AF for ≥48 h or for unknown duration who do not receive anticoagulation have a relatively high risk of stroke with cardioversion (0–7%) [50]. The addition of anticoagulation for 3–4 weeks prior and for 4 weeks after cardioversion can reduce that stroke risk to less than 1% [50]. After cardioversion, anticoagulation is important as there is a delay in the return of atrial mechanical function [51], which can promote formation of left atrial appendage thrombus. Another strategy that can reduce the time until cardioversion is to use a transesophageal echocardiogram to look for atrial clot prior to cardioversion (Figure 3). Patients still need to be fully anticoagulated at the time of and for 4 weeks after cardioversion. This approach was evaluated through the Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) trial [52]. Investigators randomized 1034 patients with AF for over 2 days duration to a transesophageal echocardiography (TEE)-guided strategy prior to cardioversion or a traditional strategy with 3 weeks of therapeutic warfarin (INR 2–3) before cardioversion. Both groups received 4 weeks of warfarin following cardioversion. The primary outcome was a composite of stroke, TIA and peripheral embolism at 6 months follow-up. There was no statistically significant difference between the two groups (p = 0.11). As a result of this and similar studies [53,54], a TEE-guided strategy is now commonly accepted.

With the recent introduction of dabigatran, many clinicians are wondering if treatment with dabigatran can be used prior to and after cardioversion to decrease the risk of stroke in patients with AF. The most comprehensive data are from a substudy of the RE-LY trial, which looked at all patients who underwent cardioversion during their participation [55]. The study protocol recommended maintenance of the assigned study drug during cardioversion. A total of 1983 cardioversions were performed: 647 in the dabigatran 110-mg twice-daily group (D110), 672 in the dabigatran 150-mg twice-daily group (D150) and 664 in the warfarin group. TEE was performed before 25.5, 24.1 and 13.3% of cardioversions in the D110, D150 and warfarin groups, respectively. There was no significant difference in the incidence of left atrial thrombus. The rate of systemic stroke was low in all groups (0.8, 0.3 and 0.6% in the D110, D150 and warfarin groups, respectively) and was not significantly different between the groups (p = 0.45). Thus, it appears that dabigatran is safe to use as anticoagulation prior to and after cardioversion. Repeat studies will be needed to confirm this assertion. Other alternatives to warfarin and dabigatran are under active investigation and appear promising [56,57].

Five-year view

Atrial fibrillation is a common cardiac arrhythmia that will increasingly affect the elderly population in coming years. The more difficult decisions for providers caring for these patients will focus around the question of which patients should be managed with a rhythm control strategy (as opposed to ventricular rate control) and how to reduce stroke risk in an aging population. Safer and more efficacious antiarrhythmic agents will need to

Key issues

- Atrial fibrillation (AF) is the most common cardiac arrhythmia and increases in prevalence with increasing age.
- AF is thought to result from a 'trigger and substrate' model. The trigger is most often ectopic beats originating in the pulmonary veins. The substrate is the result of electrical and mechanical remodeling of the atria, which allows the propagation of AF.
- Ventricular rate control is the most commonly utilized strategy to control patients with AF. It is shown to be effective in the majority of patients. However, patients with persistent symptoms, poor ventricular rate control and heart failure may benefit from a rhythm control strategy, using medication and/or pulmonary vein isolation.
- Ischemic stroke causes much of the morbidity associated with AF. Patients should be risk stratified according to their stroke risk. Using the CHADS2 system, patients with a CHADS score of 1 are considered moderate risk and have the option of warfarin anticoagulation or aspirin. Patients with a CHADS2 score of ≥2 are considered high risk and benefit from chronic warfarin anticoagulation. All patients should be counseled regarding their risk of ischemic stroke versus their risk of bleeding on anticoagulation versus aspirin. CHA2DS-VASc may help to further define those with CHADS2 scores of 1.
- Anticoagulation is an important part of cardioversion in patients with AF. 3 weeks of therapeutic warfarin prior to cardioversion versus short-term anticoagulation and transesophageal echocardiography to assess for atrial thrombus appear to be equivalent strategies in reducing the risk of stroke. All patients require anticoagulation for 4 weeks after cardioversion secondary to left atrial appendage stunning. Subsequent anticoagulation is directed by CHADS2 score.
- Dabigatran is a new oral direct thrombin inhibitor that was recently approved to prevent thromboembolic events in patients with AF. At the 150-mg twice-daily dosing, it appears to be more effective than warfarin at preventing ischemic events and has a similar bleeding risk profile. Early data suggest that dabigatran is effective at reducing stroke risk before and after cardioversion.

be developed before rhythm control management becomes the primary therapy for control of AF. In addition, more studies on the safety and efficacy of dabigatran and other alternatives to warfarin will need to be performed to further characterize their role in AF patients. Over the next 5 years, we will likely see a shift from warfarin to increasing use of these alternative agents to prevent stroke in AF patients.

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