Managing Atrial Fibrillation

Insights Into Pathophysiology, Advances in Treatment
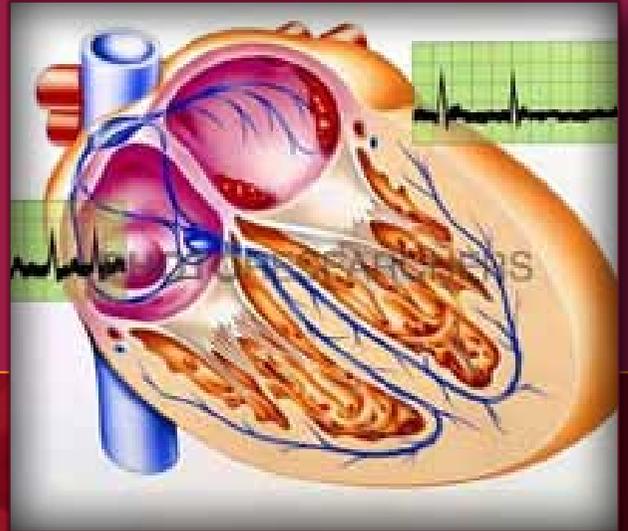
EDITOR'S NOTE

Atrial fibrillation (AF) is a common cardiac arrhythmia. With the aging of the population, AF is projected to reach epidemic proportions before the end of the first half of this century. New insights into its pathophysiology, combined with advances in treatment, have led to new guidelines on its management by leading professional organizations. The growth in various catheter and surgical therapies for AF, along with new information on this disorder, were the impetus for the creation of this monograph in an effort to provide physicians and other health care providers with a concise overview of the topic and the latest information on therapy based on recently published, revised guidelines.

In the first article, Dr Samuel Wann, Chair of the 2010 writing committee of the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society (ACCF/AHA/HRS) Focused Update on the Management of Patients with Atrial Fibrillation (updating the 2006 Guideline), reviews the epidemiology and pathophysiology of AF. In the following article, Dr Richard Lee from Northwestern University Feinberg School of Medicine discusses the prevention of complications of AF and explores issues related to oral anticoagulation. The final article by Dr Andrea Natale's group from Austin, Texas, is an excellent overview of the latest revisions of the guidelines and a critical comparison of American and European guidelines. Each topic is followed by self-assessment questions based on the content of the article.

I would like to thank the authors for their diligence in preparing their manuscripts in the short time that was available to them. My special thanks to the American College of Chest Physicians for making this possible.

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Epidemiology and Pathophysiology of Atrial Fibrillation

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Atrial fibrillation (AF) is by far the most common sustained cardiac dysrhythmia, affecting 1% to 2% of the general population. More than 6 million Americans today have AF. The incidence of AF increases with age. As the "baby boom" generation grows older, the number of patients presenting with AF is increasing dramatically. By 2050, 15.9 million patients in the United States are expected to be affected by AF. One in four men and women now 40 years old can expect to develop AF within their lifetime.[1]

Etiology and Pathology

More than 100 years ago, Sir James Mackenzie described an irregularity associated with disappearance of the "a" wave from the jugular pulse and paralysis of the atria. With the development of electrocardiography, this abnormality in atrial mechanical function was demonstrated to be due to abnormal electrical activity in the atria.

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Although the etiology and pathophysiology of AF remain incompletely understood, we now recognize that certain anatomic, electrophysiologic, and biochemical changes all contribute to the initiation and perpetuation of AF. Almost any kind of structural heart disease can trigger the process that leads to AF. AF may have a hereditary component, especially when the onset occurs at an early age. Numerous inherited cardiac syndromes, both structural and primarily electrical, have been implicated.

Associated Conditions

Increasing age, hypertension, congestive heart failure, diabetes mellitus, obesity, and valvular heart disease are all commonly associated with AF. Chronic obstructive pulmonary disease, sleep apnea, thyroid dysfunction, chronic renal disease, atrial septal defect, coronary disease, and cardiomyopathy may also be present, either as causative or complicating factors. Mental stress, excessive alcohol use, nicotine, and cocaine have all been implicated in the precipitation of AF.[1–3]

Gender and Ethnic Factors

Although fewer women than men are affected by AF, women are more often symptomatic. After correction for comorbidities, Caucasians have a higher incidence of AF than African Americans.[1–3]

AF Over Time

As AF develops, alterations occur in gene expression, hormone regulation, and distribution of cellular ionic channels. Energy production and expenditure are recalibrated. A rapid atrial rate increases cellular calcium loading and reduces cell viability, leading relatively quickly to changes in the genetic control of calcium homeostasis, shorter action potentials, a shorter atrial refractory period, and an increased vulnerability to the development of AF. Irreversible, maladaptive fibrosis and dilatation of the atria lead to electrical remodeling. Electrical remodeling itself leads to a progression from paroxysmal to persistent AF, a lower likelihood of conversion to sinus rhythm, and perpetuation of AF. Although remodeling of the left atrium may not be the primary cause of AF, it does play a fundamental role in the dynamic process leading from paroxysmal to persistent AF. AF begets AF.

Symptoms of AF

AF is often "silent," occurring without symptoms in as many as one third of patients. When present, symptoms commonly

include palpitations, dyspnea, fatigue, lightheadedness, and decreased exercise tolerance. Death rates are doubled in the presence of AF, independent of other known risk factors. Early detection of asymptomatic AF may lead to effective treatment and avoidance of adverse outcomes.[2]

Complications

Stroke caused by thromboembolism (TE) is the most serious complication of AF, occurring in 5% of nonanticoagulated patients every year. The risk of stroke increases dramatically with age. Individuals with AF aged 50 to 59 years have a 1.5% risk of stroke, while patients with AF aged 80 to 89 years have a 23.5% risk. Stroke is the third most common cause of death in the United States.

In the absence of anticoagulation, clinically evident TE occurs in approximately 1% to 2% of patients within the first month after AF of more than 48 hours duration reverts to normal sinus rhythm. While the return of synchronous atrial contraction may cause dislodgement of preformed atrial thrombi, atrial thrombi can also form after conversion of AF to sinus rhythm. Atrial stunning may result in delayed return of atrial contractility. Stagnant blood flow may persist within the atrial appendage despite restoration of normal electrical activation. Many patients have recurrent, often asymptomatic, episodes of

paroxysmal AF after "successful" restoration of sinus rhythm.

AF may also aggravate heart failure and ischemic heart disease. Tachycardia and loss of the active atrial component of ventricular filling are important symptomatic and functional elements in many patients.[3] ∎

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Self-Assessment Questions

1. Atrial fibrillation (AF) is an important public health problem because it:

   a. Often results in absenteeism in the workplace
   b. Is a common cause of stroke in the elderly
   c. Frequently causes syncope
   d. Often deteriorates into ventricular fibrillation
   e. Is the result of environmental contamination

Answer (b): Atrial fibrillation occurs most commonly in the elderly. Even when there are no premonitory symptoms, AF may result in embolic stroke. Syncope is uncommon in AF, and life-threatening arrhythmias are very rare. Environmental toxins have not been implicated.[1]

2. The most common antecedent of persistent AF is:

   a. Hyperthyroidism
   b. Obesity
   c. Acute myocardial infarction
   d. Paroxysmal AF
   e. Wolff-Parkinson-White syndrome
   f. Cigarette smoking

Answer (d): AF begets AF, regardless of etiology. The other processes included above may be associated with AF, but persistent AF is often preceded by paroxysmal AF, regardless of the underlying disease process.[1]

3. From a public health standpoint, the most important complication of AF is:

   a. Stroke
   b. Heart failure
   c. Mitral regurgitation
   d. Acute myocardial infarction
   e. Syncope

Answer (a): Stroke in AF is often severe and results in long-term disability or death. One fifth of all strokes are due to AF, which is often undiagnosed or untreated prior to the stroke.[1]

Atrial Fibrillation: Prevention of Complications

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Congestive heart failure (CHF) and thromboembolism (TE) are the primary complications of AF. Historically, CHF has been treated by rate control, and TE has been treated by anticoagulation. However, evolving work in the area of rhythm control offers the potential for improved outcomes. This section discusses the complications of AF in a framework of current and emerging options.

Preventing CHF

Patients with AF suffer a myriad of symptoms, including shortness of breath, lightheadedness, chest pressure, and fatigue. Acutely, two mechanisms contribute. Tachycardia shortens diastole, limits filling time, reduces end-diastolic volumes, and thus, decreases cardiac output. In addition, atrial contraction is lost; this may reduce cardiac output by 15% to 40%, depending on the extent of underlying ventricular disease. Chronically, tachycardia-associated cardiomyopathy follows.

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Rate Control

Rate control depresses conduction through the atrioventricular (AV) node. Limiting the peak heart rate acutely prolongs diastolic filling time and reduces chronic tachycardia-associated cardiomyopathy. Current guidelines recommend a ventricular rate of 60 to 80 beats per minute at rest and 90 to 115 beats per minute during exercise.[1] However, the optimal target heart rate remains unknown; tight control of AF with a resting heart rate below 80 may not offer benefit, compared with a strategy that allows for a faster resting heart rate.[2,3]

In establishing rate control, three classes of drugs are generally used: ß-blockers, nondihydropyridine calcium antagonists, and digoxin.[3] In the absence of pre-excitation, ß-blockers and calcium blockers are the initial drugs of choice.[3] In patients who are refractory to all medical management, AV nodal ablation and pacemaker placement may be considered. However, if AV nodal ablation is pursued, a biventricular pacing strategy should also be considered.[4]

Rhythm Control

Rhythm control attempts to restore the atrial contribution to cardiac output; this can be done with pharmacologic or mechanical therapy. Although recent-onset AF spontaneously reverts to sinus rhythm within 24 hours in at least 50% of patients, Vaughan-Williams class IA, IC, and III antiarrhythmic drugs are commonly used for cardioversion and sinus maintenance.[4]

Pharmacologic rhythm control is superior to placebo for both rate control and reduction of cardiovascular rehospitalization and mortality.[5] In patients with heart failure and AF, only amiodarone and dofetilide are recommended, as patients with CHF are particularly prone to ventricular proarrhythmic effects and negative inotropic actions of antiarrhythmic drugs.[1]

Mechanical options for cardioversion begin with synchronized electrical cardioversion, with or without pharmacologic agents. It is useful acutely in patients with hemodynamic compromise or for patients in whom AF has been prolonged.

Patients who are in AF for less than 48 hours are eligible for early cardioversion; after 48 hours, anticoagulation for a minimum of 3 weeks before and 4 weeks after cardioversion should be done to decrease the risk of TE.[6] Alternatively, a transesophageal echo can be performed to look for clots in the left atrium, and earlier cardioversion can be attempted. Since the site of thrombus is most

frequently in the left atrial appendage (LAA), an evaluation of this structure is crucial.

Advances in other forms of mechanical therapy such as catheter ablation have brought traditional therapies into question. Since the triggers of paroxysmal AF arise from the pulmonary veins in 90% of the patients, creating scar around the pulmonary veins blocks aberrant conduction and preserves sinus rhythm.[7] Currently, the Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arryhmia Society (HRS/EHRA/ECAS) expert consensus recommends this approach for symptomatic patients with AF refractory or intolerant to at least one class 1 or class 3 antiarrhythmic medication, or as first-line therapy in selected patients with CHF.[8]

Several randomized trials have demonstrated excellent rates of sinus restoration and improvement of symptoms, with success ranging from 56% to 86%.[9–11] Although this therapy is evolving, it may offer a benefit over a rate-control strategy.

Surgery for AF is the most invasive option; it also offers the highest efficacy. The Maze procedure was developed to interrupt all macroreentrant circuits that might potentially develop in the atria by creating a series of linear scars, resembling a child's "maze," on the right and left atria. This created a single pathway for the impulse to conduct from the sinus node to AV node.[12] As technology evolved, new energy sources reliably created scar without the need

to cut and sew the tissue together and made performing a Maze safer; most notably, these include radiofrequency and cryothermia.[13]

Therefore, the guidelines recommend that all patients with AF undergoing cardiac surgery should be considered if the risk of ablation is low. In an experienced center, this should be about 90% of the patients.[14]

New technology has also led to the creation of minimally invasive stand-alone surgical ablation. Although it is still early in follow-up, this procedure may offer a success rate as high as 90%, even in patients in whom catheter ablation has failed.[15]

Rate Control Versus Rhythm Control

Despite the seemingly intuitive concept that rhythm restoration should be superior to rate control, medical trials have not supported one strategy over the other.

For outcome measures of mortality and quality of life, several trials have demonstrated no inferiority of rate control compared to rhythm control.[16-18] Most notable of these studies is the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM), a 4,060-patient randomized prospective study based on intent to control rate or restore rhythm. There was no difference in survival between arms. However, certain population subsets, such as patients with left ventricular dysfunction, did appear to benefit from rhythm control. Other studies, such as Maintenance of Sinus Rhythm and Survival in Patients

With Heart Failure and Atrial Fibrillation (AF-CHF), did not find a difference between strategies.[19]

Secondary endpoints have been equivocal as well. Patients treated with a rhythm-control strategy were more frequently hospitalized in AFFIRM, How to Treat Chronic Atrial Fibrillation (HOT CAFI), and the Pharmacological Intervention in Atrial Fibrillation (PIAF) trials.[17,20] Although PIAF patients in a rhythm-control strategy had a better exercise performance, they did not experience improvement of symptoms or better quality of life.

Proponents of rhythm control argue that the actual success rate of sinus restoration in medical trials rarely exceeds 60% and is not much better than the rate of sinus restoration in the rate-control arm (usually around 40%). Further, on subsequent on-treatment analysis of the AFFIRM trial, the successful restoration of sinus rhythm was a significant predictor of survival, whereas the use of antiarrhythmic drugs increased mortality by 49%, suggesting that the benefit of sinus rhythm may be offset by the adverse effects of antiarrhythmic drugs.[21] At present, the medical data support the use of rate control in patients who are asymptomatic.

Future Directions

At present, the evidence supports the traditional rate-control strategy in asymptomatic patients. Several trials that compare catheter ablation to other medical therapy are under way. As more symptomatic patients receive benefit from

mechanical techniques to restore sinus rhythm, a change in the paradigm may evolve.

Preventing Thromboembolism

Thromboembolism is the most devastating complication of AF. Strokes from AF tend to be larger and more fatal than other types of strokes. AF is the second leading cause of stroke and accounts for 10% to 15% of all strokes each year.[22] Anticoagulation is effective in reducing stroke. The two most commonly utilized agents are aspirin and warfarin. Aspirin reduces stroke by 28%, compared with placebo. Warfarin reduces the risk of stroke by two thirds.[23,24] The decision to treat a patient with anticoagulation depends on the balance between the risk of TE and the risk of bleeding in each patient. Unfortunately, many of these risk factors overlap.

The Risk of Stroke

Several risk-stratification schemes have been developed. The most frequently employed is the $CHADS_2$ system (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke), developed according to the multivariate analysis of data from the initial large randomized trials: the Atrial Fibrillation Investigators (AFI) and the Stroke Prevention in Atrial Fibrillation (SPAF).[25,26] In $CHADS_2$, a point is given for each of several risk factors: history of CHF, hypertension, age >75 years, and diabetes mellitus. Two points are given for a history of stroke. The points are added, and the patients are stratified into groups. The risk

of annual stroke ranges from 1.9% ($CHADS_2$=0 points) to 18.2% ($CHADS_2$=6 points). The majority of patients fall in the intermediate range (1–3 points), with a risk of stroke from 2.8% to 5.9%.[1] An expert opinion panel developed a guideline for anticoagulation in AF for the American College of Chest Physicians (ACCP) that is currently a reasonable approach.[6]

Emerging Data on Thromboembolic Risk

As with any classification score, the $CHADS_2$ system is limited. Recently, in an effort to more accurately quantify risk, a similar system has been studied, the CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years [doubled], Diabetes mellitus, Stroke [doubled], Vascular disease, Age 65–74 years, and Sex category [female]). An age of 65 to 74 years receives 1 point; an age of 75 and above receives 2 points. Vascular disease and female sex each generate an additional point.

In a study of 73,538 patients with nonvalvular AF, the CHA_2DS_2-VASc performed better than the $CHADS_2$ in predicting patients at high risk and low risk.[27] Therefore, this or a similar classification system may become the future standard and provide better information to guide anticoagulation in patients with AF.

The Risk of Bleeding

Unfortunately, patients who are anticoagulated also have an increased risk of bleeding. Several risk-scoring systems have been developed. In a study of 7,329 patients

from the Stroke Prevention Using an Oral Thrombin Inhibitor in Atrial Fibrillation (SPORTIF), the HAS-BLED (Hypertension, Abnormal Renal/Liver function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concommittantly) system was the most reliable.[28] By multivariate analysis, significant predictors of bleeding were concurrent aspirin use, age 75 years or older, diabetes, and heart failure or left ventricular dysfunction. This creates a clinical dilemma. Each of the $CHADS_2$ risk factors for stroke is a risk factor for bleeding as well. Individual histories and judgments must be taken into account.

Emerging Alternatives to Warfarin

Although warfarin is effective in reducing TE, several characteristics have limited its application. In fact, in patients discharged from the hospital in AF, only half are discharged on warfarin.[13] Attempts are under way to devise alternate strategies that require less intensive monitoring and have more predictable dose-response curves.

Clopidogrel has been more incrementally beneficial than aspirin alone, but remains inferior to warfarin.[29] Most recently, dabigatran was approved. This drug may be comparable to warfarin in its ability to reduce thromboembolic events, with a lower risk of bleeding complications and no need for frequent monitoring of the serum level.[30] This is potentially an exciting advance, but more experience is needed to define the drug's long-term role.

Mechanical Alternatives to Anticoagulation

Sinus restoration after catheter ablation or surgery may reduce the risk of stroke. Although data are emerging, it may be safe to discontinue anticoagulation late after successful catheter ablation.[31] At present, the consensus is to continue anticoagulation in patients at high risk of stroke (CHADS$_2$ score of 2 or greater), even after successful ablation.[8] After cardiac surgery for AF, anticoagulation is routinely discontinued after success is determined.

Although documented only in nonrandomized series, surgery appears to reduce the risk of stroke. This may be due, in part, to the routine removal of the LAA.[8] This insight has led to initial trials of endocardial exclusion of the LAA as an alternative to anticoagulation.[32] Preliminary results are promising.

Summary

Rate control and anticoagulation remain the standard of care for asymptomatic patients who have AF. However, emerging data suggest that, in symptomatic patients, rhythm control may offer some benefits.

As technology continues to evolve, a growth in mechanical interventions, such as catheter ablation and surgery, offers hope that we will continue to increase the quality of life and, possibly, survival in many patients afflicted with this disease. ■

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Self-Assessment Questions

1. **In evaluating the risk of stroke in a patient with atrial fibrillation (AF), the single greatest risk factor is:**

    a. A history of hypertension
    b. Age 65 years or greater
    c. A history of stroke
    d. Type I diabetes mellitus
    e. A history of congestive heart failure

    Answer (c): In both the $CHADS_2$ and the CHA_2DS_2-VASc risk-scoring systems, a history of stroke is given 2 points. All other variables are given 1 point. In the CHA_2DS_2-VASc scoring system, age greater than 75 years is given 2 points. In the $CHADS_2$ system, age greater than 75 years is given 1 point. When patients are 65 to 75 years old, they receive 0 points in $CHADS_2$ and 1 point in CHA_2DS_2-VASc.[1,6,24,26]

2. **Warfarin is effective at reducing the risk of thromboembolic events. Without warfarin, the risk of stroke is roughly:**

    a. 25% higher
    b. 45% higher
    c. 65% higher
    d. 85% higher

    Answer (c): Warfarin reduces the risk of thromboembolism by roughly two thirds.[22,23]

3. **Medical therapy has clearly shown that, compared to a rate-control strategy, a rhythm-control strategy:**

    a. Improves quality of life
    b. Increases hospitalizations
    c. Improves survival
    d. Decreases medical costs

    Answer (b): Although there are multiple limitations to the current literature, such as a relatively poor success rate of sinus conversion, there has been little benefit demonstrated with a medical rhythm-control strategy. However, patients are more likely to be hospitalized more frequently.[16–20]

4. **Indications for catheter or surgical ablation for AF in symptomatic patients include:**

    a. Failure of a class 1 or 3 antiarrhythmic medication
    b. Failure of a class 2 or 4 antiarrhythmic medication
    c. Prior stroke
    d. A $CHADS_2$ score >2

    Answer (a): Indications for catheter ablation include: failure of at least one class 1 or 3 antiarrhythmic medication or first line in selected patients with CHF. Because there is a risk of stroke associated with catheter ablation, a history of stroke or a high risk of periprocedural stroke (essentially $CHADS_2$ risk factors) are relative contraindications to a catheter-ablation procedure. At present, these patients may still be good candidates for surgical ablation.[8]

Updated International Guidelines on the Management of Atrial Fibrillation

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Since the last release of international guidelines on the management of atrial fibrillation (AF) in 2006,[1] important advances in pharmacologic and nonpharmacologic treatments have significantly expanded the therapeutic armamentarium against this arrhythmia. In light of such advances, American and European cardiovascular societies have updated their guidelines.[2-4] Notably, European societies for the first time have drafted separate

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guidelines more consistent with clinical practice in European countries.[3]

This article will review major changes in the recommendations included in recently updated international guidelines on AF management, highlighting their potential impact on clinical practice.

Pharmacologic Therapy

The previous edition of AF guidelines recommended many classical antiarrhythmic agents for restoring and maintaining sinus rhythm.[1] Classical antiarrhythmic agents, however, are of limited effectiveness and are accompanied by potentially serious side effects.[2,3]

The most important recent advance in antifibrillatory drug therapy is dronedarone, an analogue of amiodarone. The landmark study leading to dronedarone approval has been ATHENA (A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation), a placebo-controlled trial of more than 4,000 subjects with AF and additional risk factors for mortality. ATHENA is the first antiarrhythmic drug trial with adequate power to assess morbidity and mortality.[5] After a mean follow-up of 21 ± 5 months, 31.9% of patients allocated to dronedarone reached

the composite primary endpoint of hospitalization for cardiovascular cause or death from any cause, compared with 39.4% of patients receiving placebo. The benefit of dronedarone was largely driven by a reduction of cardiovascular hospitalizations, whereas no significant reduction in all-cause mortality was observed (**FIGURE 1**).

Although such results are important, the lack of comparison with an active antiarrhythmic drug is a major weakness of the ATHENA trial, and the real incremental value of dronedarone, compared with other available antiarrhythmic agents, remains to be established.

International bodies have incorporated evidence on dronedarone and produced quite different recommendations.[2,3] European guidelines recommend dronedarone for sinus-rhythm maintenance across a spectrum of patients with AF with or without structural heart disease, with the exception of patients with advanced heart failure or recent heart-failure decompensation.[3] This recommendation was driven by the results of another placebo-controlled trial of dronedarone in patients with recently decompensated heart failure; the trial was stopped early for excess mortality in the dronedarone arm.[6]

In contrast, American societies recommend dronedarone as a reasonable therapy to decrease the need for hospitalization for cardiovascular events in ATHENA-like patients, contraindicating administration to patients with advanced heart failure.[2]

Rate-Control Strategies for AF

Updated guidelines continue to support the notion that rate- and rhythm-control strategies are equivalent in terms of major outcomes, including death and hospitalization, heart-failure events, and quality of life.[2,3] This concept derived from large pharmacologic trials conducted nearly 10 years ago that reported no difference between rate- and rhythm-control therapies in regard to such outcomes.[1-3] However, none of the large AF-treatment trials definitively demonstrated effective and long-term consistency of sinus-rhythm maintenance in patients allocated to a rhythm-control strategy. Therefore, no conclusion at all can be drawn from these studies as to whether an effective rhythm-control therapy is equivalent to a rate-control strategy. However, there is strong evidence for causality between AF and worse outcomes from case-control studies, and subgroup analyses of large trials on AF treatment have shown that persistence of sinus rhythm is associated with improved survival.[7]

Taken together, these findings raise the suspicion that results of rate- vs rhythm-control trials may have been misinterpreted. To this

Effect of Dronedarone on Cardiovascular (CV) Events in Atrial Fibrillation in the ATHENA Trial[5]
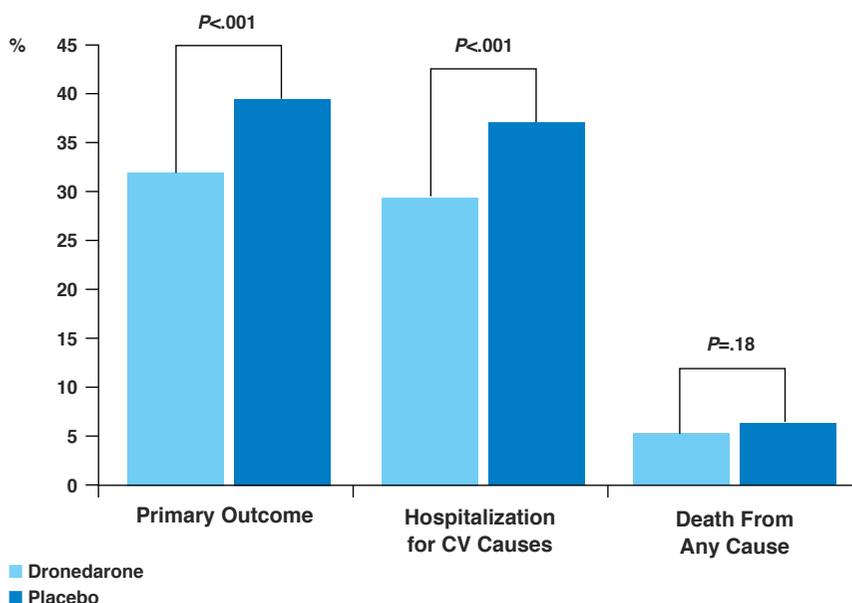
ATHENA=A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation.

Source: Hohnloser et al.[5]

regard, the ATHENA trial, which tested a barely effective antifibrillatory agent with a high safety profile, provided the first evidence-based signal that maintaining sinus rhythm in a safe manner may actually prevent major adverse outcomes in AF.[5]

The optimal level of heart-rate control to reduce symptoms and improve hemodynamics is still unclear in rate-control strategies. The recently published RACE II (Rate Control Efficacy in Permanent Atrial Fibrillation II) trial failed to show an incremental benefit of strict over lenient rate-control therapy.[8] In this trial, 614 patients with permanent AF were randomized to rate-control therapy with a target heart rate below 110 beats per minute (lenient rate-control arm), or to a target heart rate below 80 beats per minute (stringent rate-control arm). After a maximum follow-up of 3 years, the estimated cumulative incidence of the primary outcome (composite of death from cardiovascular causes, hospitalization for heart failure, thromboembolism, bleeding, and life-threatening arrhythmic events) was 12.9% in the lenient-control group and 14.9% in the strict-control group. It is important to emphasize that only 15% of the patients included in the RACE II trial had poor left

FIGURE 2

Anticoagulation Recommendations for Stroke Prevention in Atrial Fibrillation
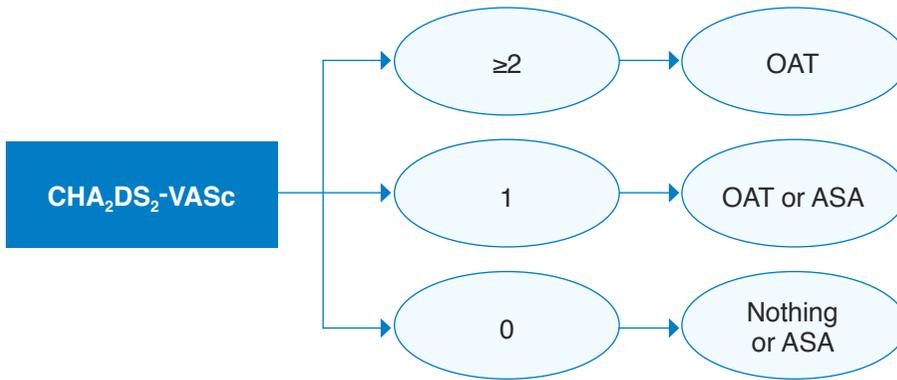
OAT=oral anticoagulant therapy; ASA=aspirin

How to score: C=congestive heart failure/left ventricular dysfunction, 1 point; H=hypertension, 1 point; A=age ≥75 years, 1 point; D=diabetes mellitus, 1 point; S=stroke/transient ischemic attack/thromboembolism, 2 points; V=vascular disease, 1 point; A=age 65–74 years, 1 point; S=female sex, 1 point.

Source: European Heart Rhythm Association et al.[3]

ventricular function (ie, ejection fraction ≤40%), and the benefit of a more stringent rate-control strategy in these patients warrants further investigation. Updated guidelines take these results into account and suggest a lenient rate-control strategy in patients with persistent AF without significant left ventricular dysfunction.

The results of RACE II should be treated with caution. One fourth of the patients allocated to a strict rate-control strategy failed to reach the target heart rate because of drug-related adverse effects, which may have confounded endpoint assessment. Moreover, RACE II results may not be applicable to highly symptomatic patients who require more aggressive heart-rate reduction or an attempt at restoration of sinus rhythm.

## Pharmacologic Therapy of AF: Antithrombotic Drugs

Proper anticoagulation is the mainstay of treatment of AF to avoid thromboembolic complications. European guidelines have emphasized the importance of patient selection for oral anticoagulant therapy (OAT) through a systematic assessment of individual thromboembolic and hemorrhagic risks.[3] The CHADS$_2$ (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke) score has been adopted by previous guidelines to weigh individual thromboembolic risk and has been widely implemented in clinical practice due the ease of its format. Patients with a CHADS$_2$ score ≥2 are classified as being at high risk of thromboembolism and should receive OAT. However, nearly two thirds of the patients fall into the range of intermediate risk (ie, CHADS$_2$ score=1), which complicates the question of whether OAT is appropriate.[3] Moreover, other risk factors for thromboembolism, such as female sex and vascular heart disease, were not included in the CHADS$_2$ score. To overcome limitations of the CHADS$_2$ score, European guidelines have introduced a new assessment tool—namely, the CHA$_2$DS$_2$-VASc (Congestive heart failure, Hypertension, Age ≥75 years [doubled], Diabetes mellitus, Stroke [doubled], Vascular disease, Age 65 to 74 years, and Sex category [female]). This tool includes among risk factors an age of 65–74 years, female sex, and presence of vascular heart disease.[3] A score ≥2 is still necessary to recommend OAT, and OAT is preferred even for those patients with a score of 1 (**FIGURE 2**). No data are available to define the real thromboembolic risk of patients who have a score of 0, although it is entirely plausible that they retain increased risk, as in the case of patients with a CHADS$_2$ score of 0 (**FIGURE 3**).

Applying the CHA$_2$DS$_2$-VASc score, more patients with AF will qualify for OAT (**FIGURE 3**). Disturbingly, OAT with warfarin still appears to be underused, with only 30% to 60% of eligible patients actually receiving therapy.[9]

European guidelines have also focused on the competing risk of

FIGURE 3

Adjusted Rate of Stroke According to CHADS$_2$ and CHA$_2$DS$_2$-VASc Scores
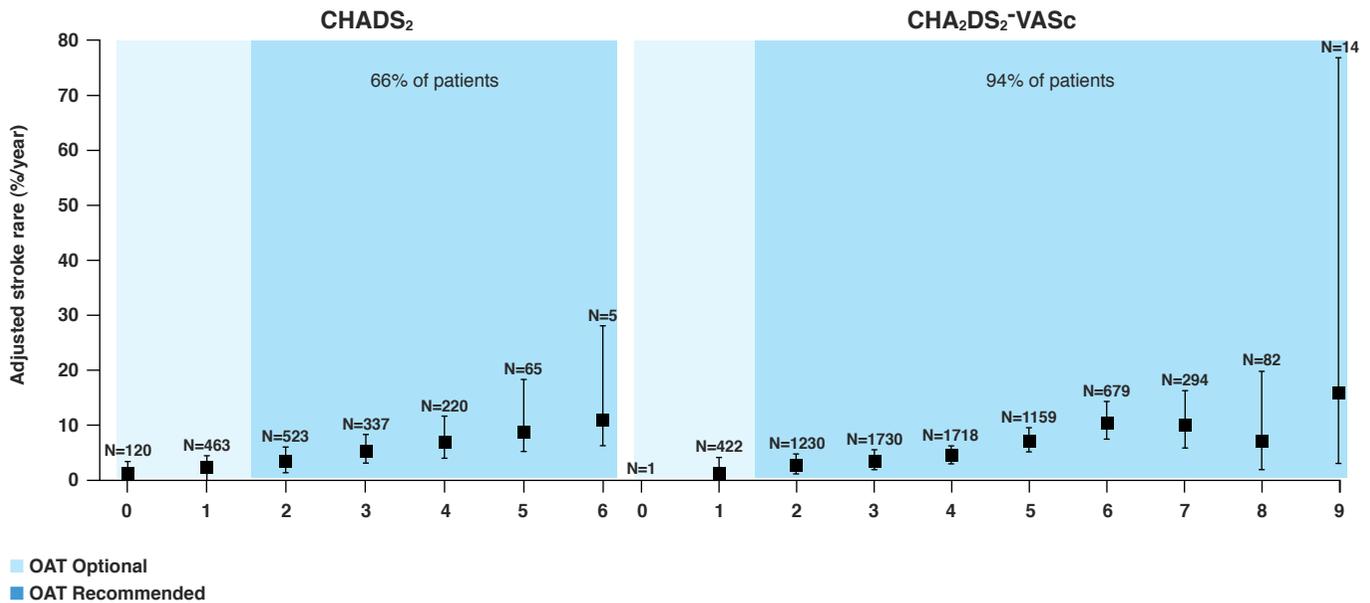
Square boxes denote yearly stroke rates; vertical lines represent 95% confidence intervals. Data are from the NRAF registry[18] and from the SPORTIF III and V trials.[19] No data are available to assess the thromboembolic risk for patients with a CHA$_2$DS$_2$-VASc score of 0. Applying the CHA$_2$DS$_2$-VASc score, more patients with atrial fibrillation qualify for OAT (94% vs 66%).

CHADS$_2$=Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Stroke; CHA$_2$DS$_2$-VASc=Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes mellitus, Stroke (doubled), Vascular disease, Age 65–74, and Sex category (female); NRAF=National Registry of Atrial Fibrillation; OAT=oral anticoagulant therapy; SPORTIF=Stroke Prevention using Oral Thrombin Inhibitor in atrial Fibrillation.

Sources: Gage et al[18]; Lip et al.[19]

bleeding from OAT. This is a particularly challenging issue, since many thromboembolic risk factors are also risk factors for bleeding. A score, namely, the HAS-BLED (Hypertension, Abnormal renal or liver function, Stroke, Bleeding, Labile INRs, Elderly [age >65 years], Drugs or alcohol) has been developed; OAT should be administered with caution in patients who have a HAS-BLED score ≥3.[3]

Relevant updates in antithrombotic therapy have also been included in the latest guidelines, although American and European societies gave different recommendations in this setting.[2-4] The oral direct thrombin inhibitor dabigatran etexilate has been US Food and Drug Administration (FDA)-approved for prevention of TE in nonvalvular AF. The landmark study leading to approval was the RE-LY trial (Randomized Evaluation of Long-term anticoagulant therapy).[10] RE-LY compared two dosages of dabigatran (110 mg and 150 mg twice daily) against open-label warfarin in a noninfe-

riority trial including more than 18,000 patients with AF and a CHADS$_2$ score ≥1. The composite endpoint of stroke or systemic TE was reached in 1.69% of patients/year in the warfarin group, in 1.53% of patients/year in the dabigatran 110-mg (twice daily) group (P<.001 for noninferiority), and in 1.22% of patients/year in the dabigatran 150-mg (twice daily) group (P<.001 for superiority). Quite surprisingly, the rate of hemorrhagic stroke was inferior with both dosages of dabigatran,

TABLE

Updated Recommendation for Catheter Ablation of Atrial Fibrillation (AF)

Clinical Scenario	2006 Guidelines[1]		2010 Guidelines[2]		
	Class of Recommendation	Level of Evidence	Class of Recommendation	Level of Evidence	Notes
Symptomatic paroxysmal AF, failed treatment with an antiarrhythmic drug	IIa	C	I	A	Modified rec
Symptomatic persistent AF	—	—	IIa	A	New rec
Symptomatic paroxysmal AF, significant left atrial dilatation or left ventricular dysfunction	—	—	IIb	A	New rec

AAD = antiarrhythmic drug; LV = left ventricular; rec=recommendation.

Source: Wann et al.[2]

compared with warfarin, which suggests that most hemorrhagic strokes in AF may actually be thromboembolic strokes complicated by hemorrhagic effusion.

The international normalized ratio (INR) in the warfarin group was within the therapeutic range only 64% of the time. Therefore, no definitive data support the superiority of dabigatran over warfarin in patients who are well controlled on warfarin.

During the study, more patients discontinued treatment with dabigatran than warfarin. While this may be due to a higher incidence of side effects in the dabigatran arm, the open-label design of the study may have confounded this endpoint. In fact, when physicians and patients are aware of the treatment assignment, differential vigilance may occur if the supposed inferior group is more intensively monitored.

In regard to the safety of dabigatran, two findings should be emphasized: there was a significantly greater rate of myocardial infarction and a higher risk of gastrointestinal side effects (both dosages) and bleeding (150-mg) with dabigatran. Taken together, these results raise concerns about the use of dabigatran in people who are at high risk of coronary heart disease or gastrointestinal bleeding.

American guidelines offer a clear recommendation for dabigatran as an alternative to warfarin for the prevention of stroke and systemic TE in patients with non-valvular AF and thromboembolic risk factors. However, European societies only mention dabigatran tangentially, without providing a recommendation.

The role of antiplatelet therapy in TE prevention in AF has been further elucidated by updated guidelines.[2,3] Antiplatelet therapy, either single or a combination of two antiplatelet regimens,

has been shown to be inferior to OAT for thromboembolic protection in AF. Patients not suitable for warfarin, however, may benefit from dual-antiplatelet therapy with aspirin and clopidogrel. In the ACTIVE-A trial (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events), patients deemed unsuitable for OAT (due to an increased risk of bleeding or patient or physician preference) were randomized to aspirin plus clopidogrel versus aspirin plus placebo.[11] After a follow-up of 3.6 years, major vascular events occurred in 6.8% of patients/year in the aspirin plus clopidogrel group versus 7.6% of patients/year in the aspirin plus placebo group (*P*=.01 for comparison). The difference was driven by a reduction in the rate of stroke with clopidogrel. Major bleeding rates, however, were increased by dual-antiplatelet therapy. Based on these results,

American guidelines suggest that dual-antiplatelet therapy is a reasonable strategy to reduce the risk of major vascular events, including stroke, in patients with AF in whom OAT with warfarin is considered unsuitable because of patient or physician preference.[2]

Nonpharmacologic Therapy of AF: Catheter Ablation

In patients with symptomatic paroxysmal AF who have failed treatment with an antiarrhythmic drug, catheter ablation is highly reasonable and evidence-based.[12-15] Accordingly, updated American guidelines give a class I indication to catheter ablation with the highest level of evidence in these patients (**TABLE 1**).[2] Multiple randomized trials support this position. In the A4 trial (Atrial Fibrillation vs Antiarryrhthmic Drugs), 112 patients with paroxysmal AF resistant to at least one antiarrhythmic drug were randomly assigned to pulmonary vein antrum isolation or further antiarrhythmic therapy.[12] At 1 year of follow-up, 89% of the patients assigned to catheter ablation were free from AF recurrence, while only 23% of those assigned to antiarrhythmic drug therapy reached the same endpoint (P<.001 for comparison).

These encouraging results have been confirmed by larger trials. The multicenter ThermoCool AF trial randomized in 2:1 fashion a total of 167 patients with symptomatic drug-refractory AF to catheter ablation or further antiarrhythmic drug therapy.[14] Follow-up was 9 months, and the primary endpoint was a composite of any documented symptomatic AF episode, repeat ablation >80 days after the initial ablation, acute pulmonary vein reconnection, or changes in the specified drug regimen after a 3-month "blanking period." At the end of follow-up, 66% of the patients receiving catheter ablation remained free from the primary endpoint, compared with 16% of those assigned to antiarrhythmic drug therapy.

There is also evidence of superiority of catheter ablation over antiarrhythmic agents as first-line therapy in symptomatic patients with paroxysmal AF. In the RAAFT (Randomized Trial of RFA versus AAD as First-Line Treatment of Symptomatic Atrial Fibrillation) trial, 70 patients with monthly symptomatic episodes of AF for at least 3 months (96% paroxysmal AF) were randomized to pulmonary vein antrum isolation or antiarrhythmic drug therapy.[13] Outcomes assessed were recurrence of AF, hospitalization, and quality of life at 1 year. At the end of follow-up, 63% of the patients assigned to antiarrhythmic drug therapy experienced at least one recurrence of symptomatic AF, compared with 13% of those assigned to catheter ablation (P<.001). Catheter ablation was also associated with a significantly lower hospitalization rate (9% vs 54%, P<.001) and better quality of life.

Data already point to the success of catheter ablation in patients with left ventricular dysfunction,[16] previous cardiac surgery, or valvular heart disease.[17] In light of this evidence, American guidelines have raised the level of recommendation for catheter ablation in the setting of symptomatic persistent AF, significant left atrial dilatation, or significant left ventricular dysfunction (**TABLE 1**).[2]

Summary

The latest international guidelines on AF include several important updates. A new antiarrhythmic agent (dronedarone) has been introduced to reduce cardiovascular hospitalization in patients with AF undergoing rhythm-control therapy.

Emphasis has been placed on the need for more accurate assessment of individual thromboembolic and hemorrhagic risks to tailor antithrombotic treatment. Dabigatran, an oral direct thrombin inhibitor recently approved by the FDA, has been shown to be an equivalent or even superior alternative to warfarin in patients with nonvalvular AF and risk factors for TE.

Patients who are not suitable for OAT may be best managed by dual-antiplatelet therapy.

Physicians and patients should also be aware that a cure for AF may be achieved through catheter ablation, which should not be unnecessarily avoided or delayed in selected populations of patients. ∎

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Self-Assessment Questions

1. How many patients should be treated with dronedarone to avoid one hospitalization for cardiovascular cause or death over 2 years?

a. 4
b. 7
c. 8
d. 10
e. 13

Answer (e): In the ATHENA trial, after a mean follow-up of 21 ± 5 months, the primary composite endpoint of hospitalization for cardiovascular cause or death from any cause occurred in 31.9% of the patients allocated to dronedarone and in 39.4% of those receiving placebo. The absolute risk reduction associated with dronedarone is, therefore, 7.5% (39.4%-31.9%), and the number of patients needed to treat to avoid one hospitalization for cardiovascular causes or death is 13.

2. What do large pharmacologic rate- versus rhythm-control trials on atrial fibrillation (AF) demonstrate in terms of major cardiovascular outcomes?

a. Equivalence of rate-control and rhythm-control strategies
b. Noninferiority of rate-control versus rhythm-control strategy
c. Equivalence of sinus rhythm maintenance and rate control of AF
d. Equivalence of rate-control and rhythm-control pharmacologic strategies
e. Noninferiority of rate-control versus rhythm-control pharmacologic strategy

Answer (d): Large pharmacologic rate- vs rhythm-control trials on AF demonstrate equivalence between pharmacologic rhythm-control and rate-control therapies. However, none of the trials demonstrate consistent and lasting sinus rhythm maintenance in the rhythm-control arms. Therefore, no conclusion at all can be derived from such trials on the benefit of sinus rhythm maintenance (ie, effective rhythm-control therapy) in patients with AF. Of note, subgroup analyses of the AFFIRM trial suggest lower mortality rates in patients achieving persistent sinus rhythm maintenance.

3. According to the CHA$_2$DS$_2$-VASc score, what is the annual adjusted risk of stroke to qualify for oral anticoagulant therapy?

a. 1.3%
b. 2.2%
c. 3.2%
d. 4.0%
e. 6.7%

Answer (b): Analysis of data from the NRAF registry and SPORTIF III and V trials suggests that, after application of the novel CHA$_2$DS$_2$-VASc score for thromboembolic risk assessment in AF, patients who qualify for oral anticoagulant therapy (ie, score ≥2) have an annual adjusted risk of stroke of 2.2%.

4. A 61-year-old male with a 6-month history of symptomatic paroxysmal AF resistant to antiarrhythmic treatment with flecainide comes for evaluation. What is the best next step in the management of his condition?

a. Add amiodarone
b. Add dronedarone
c. Discontinue flecainide and begin propafenone plus amiodarone
d. Refer for catheter ablation
e. Discontinue flecainide and begin propafenone plus dronedarone

Answer (d): Updated guidelines for the management of patients with AF give a class 1 (level of evidence A) indication to catheter ablation in patients with symptomatic paroxysmal AF after failed treatment with at least one antiarrhythmic drug.