The Impact of New and Emerging Clinical Data on Treatment Strategies for Atrial Fibrillation

ERIC N. PRYSTOWSKY, M.D.,* JOHN CAMM, M.D.,† GREGORY Y.H. LIP, M.D.,‡
MAURITS ALLESSIE, M.D.,§ JEAN-FRANÇOIS BERGMANN, M.D.,¶,**
GÜNTER BREITHARDT, M.D.,¶ JOSEP BRUGADA, M.D.,†† HARRY CRIJNS, M.D.,†††
PATRICK T. ELLINOR, M.D., Ph.D.,§§ DANIEL MARK, M.D.,¶¶
GERALD NACCARELLI, M.D.,*** DOUGLAS PACKER, M.D.,†††† and JUAN TAMARGO, M.D.†††††

From *The Care Group, Indianapolis, Indiana, USA; †St. Georges University of London, London, UK; ‡University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, UK; §Department of Physiology, University Maastricht, Maastricht, The Netherlands; **Service de Médecine Interne A, Hôpital Lariboisière, Paris, France; ¶Department of Cardiology and Angiology, Hospital of the University of Münster, Münster, Germany; ††Arrhythmia Section, Cardiovascular Institute, Hospital Clinic, University of Barcelona, Barcelona, Spain; †††Cardiovascular Research Institute Maastricht (CARIM), Department of Cardiology, University Hospital Maastricht, Maastricht, The Netherlands; ††††Cardiovascular Research Center and Cardiac Arrhythmia Service, Massachusetts General Hospital, Boston, Massachusetts, USA; ¶¶Department of Medicine/Cardiovascular Medicine, Duke University Medical Center, Durham, North Carolina, USA; ***Division of Cardiology, Penn State Heart and Vascular Institute, Hershey, Pennsylvania, USA; ††††Mayo Clinic, Rochester, Minnesota, USA; and †††††Department of Pharmacology, Faculty of Medicine, Universidad Complutense de Madrid, Madrid, Spain

AF Treatment Strategies. Introduction: The Atrial Fibrillation (AF) Exchange Group, an international multidisciplinary group concerned with the management of AF, was convened to review recent advances in the field and the potential impact on treatment strategies.

Methods: Issues discussed included epidemiology and the impact of the rising incidence of AF on health care systems, developments in pharmacological and surgical interventions in the management of arrhythmias and thromboprophylaxis, the potential to affect treatment strategies, and barriers to implementing them.

Results: The incidence of AF and the associated burden on health care systems are increasing with aging populations, prevalence of comorbidities and more effective treatment of cardiovascular diseases. Advances in available medical treatments, in particular dronedarone and dabigatran, with other products in development, offer the possibility of changes in treatment paradigms and a greater emphasis on reducing hospitalizations and improvement in long-term outcomes instead of a symptom/safety-driven approach in which the priority is symptom suppression without provoking drug toxicity. Developments in catheter ablation techniques may mean that, in experienced centers, ablation may be offered as first-line treatment in selected patient populations. Barriers to optimal treatment include underdiagnosis, lack of recognition as a serious condition and as a risk factor for stroke, limited access to care, inadequate implementation of guidelines, and poor adherence to treatment.

Conclusions: The focus of the management of AF may be changing as a consequence of new treatments based on the outcome improvements they offer. However, the benefits will not be fully realized if guidelines and guidance are not observed in routine clinical practice. (J Cardiovasc Electrophysiol, Vol. pp. 1-13)

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Introduction

Atrial fibrillation (AF) is a major cause of hospitalization, morbidity, and mortality. The burden of AF is projected to increase in the future as a result of demographic changes, improved survival following cardiac events and associated comorbid conditions. Heart disease, due to factors such as hypertension, heart failure, and atherosclerosis, predisposes patients to AF, which in turn is associated with increased risk of severe and potentially fatal cardiovascular complications (Fig. 11-3). AF increases risk throughout the cardiovascular continuum, as it is associated with a nearly doubled risk of death⁴ and an almost 5-fold increase in the risk of stroke.⁵

Although cardiovascular disease is a worldwide problem, almost 80% of the global mortality and disease burden occurs in developing countries. Published guidelines on the management of patients with AF, such as those advocated by ACC/AHA/ESC,⁶ may not be suitable for use in these areas, and approaches to its prevention may also differ between countries for cultural, social, economic, and medical reasons.⁷

A recent NIH workshop identified gaps and recommended research strategies to prevent AF.⁸ However, the workshop provided no specific recommendations on clinical patient care. The day-to-day clinical management of AF is complex and variable, reflecting the limitations of currently available therapies as well as the heterogeneous nature of the patient population and the associated level of risk. The diagnosis and stratification of patients with AF presents further challenges but also plays a critical role in achieving optimal management of the condition. Treatment strategies for AF can be either pharmacological or nonpharmacological, and both approaches may be complicated by the presence of comorbidities such as hypertension, diabetes, and/or preexisting cardiovascular disease (heart failure, coronary artery disease). Management of AF focuses on 3 broad objectives—prevention of thromboembolism, rate control, and maintenance of sinus rhythm; however, they are not mutually exclusive.

The AF Exchange Group was convened to evaluate new evidence and strategies in the pharmacological and nonpharmacological management of AF, and to provide interpretation and guidance on the potential impact of such data on the practical management of patients with AF. The Group comprises experts in fields of cardiac arrhythmias and heart failure and also in related areas of genetic predisposition, health outcomes, and epidemiology. The inaugural meeting took place on April 19, 2009, in Paris, France, at which a series of questions were discussed that highlighted key issues in the management of AF. A second meeting to discuss primarily new research on anticoagulation and stroke prevention was held in Orlando in November 2009.

The article is divided into the following set of questions for discussion:

1. What is the incidence of AF? At what rate is it changing? Why is it changing? What are the implications for health care systems in industrialized and developing economies? Are the consequences of health care costs fully appreciated?
2. What is the newly available evidence on drug therapy to maintain sinus rhythm? How does this new evidence have the potential to change treatment algorithms? Does new evidence suggest that current stratification assessments for therapy should be changed?
3. What is the newly available evidence on catheter ablation to maintain sinus rhythm? How does this new evidence have the potential to change treatment algorithms? Does new evidence suggest that current risk stratification for therapy should be changed?
4. What are the barriers in implementing current treatment strategies?
5. Should AF treatment strategies focus on major cardiovascular outcomes rather than control of arrhythmia?
6. How can the incidence of thromboembolism and stroke be reduced?

A summary of the discussion in relation to these questions, in terms of opinions, views and any consensus reached, is reported in this article.


AF is the most common cardiac arrhythmia.⁹ The incidence and prevalence of AF has been evaluated in a number of population-based studies performed in the United States and Western Europe.⁹-¹¹ These studies have shown that the incidence and prevalence of AF increase with age are higher in men than in women. The ATRIA study also showed that the prevalence of AF in persons aged 50 years or older was higher in whites than in African Americans.⁹,⁶ However, additional research is required to determine the incidence, prevalence, risk factors, pattern of onset, progression, and prognosis of AF in non-Caucasian races and ethnicities.

The studies by Go et al.⁹ and Miyasaka et al.¹⁰ projected the prevalence of AF in the United States to increase in the future, although the actual estimates obtained from the 2 studies are quite different.⁹,¹¹ This may be due partly to differences in populations studied as well as methodological differences between the 2 studies.

A recently published study by Naccarelli et al.,¹² using a large national database, estimated the national prevalence of AF to be 3.03 million in 2005, 4.78 million in 2025, and 7.56 million in 2050, which is greater than that predicted by Go et al.,⁹ but lower than those predicted by Miyasaka et al.¹¹ The higher estimates of prevalence in the projections by Miyasaka et al. result from the inclusion of assumptions.
regarding an increase in the incidence of AF observed between 1980 and 2000.\textsuperscript{11}

Much of the predicted increase in the number of patients with AF may be due in part to the overall aging of the population, and some people have suggested that these figures may be overstating the problem. Another view is that the current estimates are too low because many patients have asymptomatic AF—especially the elderly—and they may not be included in any current prevalence studies. Thus, the true prevalence of AF in the community is unknown, and likely is systematically underestimated. In the future, it will be important to identify a more meaningful measure of the real burden of the disease in population terms. Nevertheless, irrespective of the measures that are applied, the prevalence of AF and its associated costs are clearly increasing.

It is known that AF is associated not only with older age and hypertension, but also chronic heart disease, especially heart failure, and coronary artery disease. Increasingly, successful treatment of myocardial infarction and heart failure is resulting in lower mortality rates from these cardiovascular conditions, thereby resulting in a population of patients wherein a higher incidence of AF might be expected to occur. Other contributing factors to the rising incidence of AF include the increasing prevalence of comorbidities such as obesity, hypertension, diabetes mellitus, metabolic syndrome, and chronic kidney disease.\textsuperscript{13-15}

Although these studies provide an overview of the prevalence and incidence of AF in developed countries, it must be emphasized that limited data are available for developing countries and the epidemiology of AF in nonwhite ethnic groups.

What Are the Implications for Health Care Systems in Industrialized and Developing Economies?

AF represents a significant burden to patients, ranging from the impact of debilitating symptoms on daily life to the increased risk of stroke and/or death. The mortality rate of patients with AF is approximately double that of patients with normal sinus rhythm and is linked to the severity of underlying heart disease.\textsuperscript{4} AF is also associated with a near 5-fold increase in the rate of ischemic stroke.\textsuperscript{5} Moreover, AF aggravates heart failure and, in turn, heart failure promotes AF. Individuals with either condition who develop the alternate condition share a poor prognosis.\textsuperscript{16} An increased risk of dementia has been identified in patients with AF and even in the absence of manifest stroke, AF may be associated with cognitive impairment.\textsuperscript{17,18} An inability to perform normal daily activities because of the risk of provoking or exacerbating symptoms is also likely to contribute to impaired quality of life (QoL) in patients with AF.\textsuperscript{19}

Many patients with AF are asymptomatic and appear to live normal lives. An important clinical decision for those physicians involved in the management of patients with AF is whether or not to restore and maintain sinus rhythm in a patient who feels well to try to prevent cardiovascular complications or dementia. It may be argued that asymptomatic patients should only be treated if this intervention can be shown to improve outcomes. Currently, there are observational data that AF increases stroke risk and worsens mortality rates in patients with heart failure, and there is also considerable evidence of the benefits of anticoagulation on stroke risk and all-cause mortality in patients with AF. However, there are insufficient data on the benefits of sinus rhythm on the risk of developing heart failure, dementia and other comorbidities as it is not known whether AF is a risk factor or a risk marker. Clearly, there is therefore a need to accumulate further evidence on whether maintaining sinus rhythm will improve prognosis.

If individuals with asymptomatic AF were to be identified by systematic or opportunistic ECG screening, the increased diagnosis of AF is likely to be of value because individuals with asymptomatic AF are still at increased risk of stroke, dementia, and heart failure. There is evidence from medical claims data from more than 20 million individuals that patients with nontransient AF are significantly more likely to have a number of comorbid conditions (including hypertension, chronic heart failure, coronary artery disease, and diabetes) than their matched controls.\textsuperscript{9} However, when reviewing these figures there is the caveat that most of the published information on the impact of AF has been obtained from relatively affluent developed countries in Europe and North America, and more data are needed from countries with developing economies.

Are the Consequences of AF on Health Care Costs Fully Appreciated?

Health care costs incurred by patients with AF are high and are likely to increase in the future.\textsuperscript{20} Annual costs vary widely among countries and have been reported to be between 4,000 and 14,000 US dollars in North America and between 1,000 and 3,000 Euros in Europe.\textsuperscript{21-23}
Hospitalizations due to AF are reported to have increased by 60% in the last 10 to 20 years, and AF is now the leading cause of hospitalizations for a cardiac arrhythmia. Studies have reported that hospital admissions for AF represent 4% of acute medical admissions and 8% of total cardiovascular admissions. Hospital admissions represent the single largest factor in direct costs associated with AF and approximately 50% of costs attributable to AF are due to hospitalizations.

At present, symptoms of AF are still the principal drivers of treatment even though it is known that many patients (up to 33%) have asymptomatic AF. There is a need for an objective measurement/parameter that will demonstrate whether patients with AF should be treated more or less aggressively and proactively.

**Conclusions**

Given the increasing prevalence and incidence of AF worldwide and the paucity of data regarding AF in developing countries, it is imperative that cost-effective treatment strategies be developed that reflect the capabilities of different regional health care delivery systems. It will be important to design clinical studies that examine the impact of AF therapies on health outcomes in order to be able to assess the cost-effectiveness of their use.

**What Is the Newly Available Evidence on Drug Therapy to Maintain Sinus Rhythm?**

Antiarrhythmic drugs are an important part of the management of AF. A spectrum of antiarrhythmic drugs is required so that treatment can be tailored to the needs of the individual patient according to the profile of their underlying heart disease. To be of real value in AF an antiarrhythmic drug should reduce morbidity and mortality, and the use of agents for different phases of AF prevention (primary and secondary) should also be evaluated.

**Two New Antiarrhythmic Drugs—Vernakalant and Dronedarone**

Vernakalant acts at cardiac sodium channels and several potassium channels that are expressed mainly in the atria. To date, it has been administered intravenously for cardioversion in about 700 patients with AF, was effective in about half of those patients, and demonstrated a good safety profile. Recent studies include CRAFT (a phase II dose-finding study), ACT I, ACT II, and ACT III (pivotal phase III studies), and ACT IV (a phase III safety study).

In a phase III trial, patients with short- (3 hours to 7 days) or long-lasting AF (8 to 45 days) were randomized to receive either vernakalant or placebo. Approximately one-half (51.7%) of the patients in the short-duration group who received vernakalant converted to sinus rhythm compared with 4.0% of patients who received placebo (P < 0.001). In patients with long-standing AF, vernakalant was ineffective, with effects not significantly different from placebo. The results of another phase III study indicated that vernakalant was safe and effective for AF conversion in patients with postoperative AF. Preliminary studies of oral vernakalant have also been conducted. The results from a phase Ib study of oral vernakalant in 735 patients with AF have recently been presented. Patients were randomized to oral vernakalant (150, 300, or 500 mg bid) or placebo following successful cardioversion. Within the 3-month follow-up period, the time to AF recurrence was significantly longer in the 500 mg bid vernakalant group (median > 90 days) versus 29 days in the placebo group (hazard ratio 0.735, P = 0.0275). In addition, 51.5% of patients in the 500 mg bid dosing group (n = 150) completed the study in sinus rhythm versus 37.9% in the placebo group (n = 160). Oral vernakalant was well tolerated. The rate of adverse events was similar across all of the study groups. These preliminary results suggest that oral vernakalant 500 mg bid is effective and well tolerated for the prevention of AF recurrence after cardioversion. The results from the phase III program are awaited.

Dronedarone is a potent blocker of multiple ion currents and exhibits antiadrenergic effects. Dronedarone shares many of the membrane ion channel effects of amiodarone and it has been studied in a number of clinical trials involving patients with AF, including EURIDIS and ADONIS (2 identical phase III trials, 1 European and 1 non-European), ATHENA, and DIONYSOS. DIONYSOS demonstrated that although amiodarone was significantly more effective as an antiarrhythmic drug, dronedarone was safer, as most of the significant adverse events were due to amiodarone. There were 184 patients (73.9%) who reached the primary endpoint in the dronedarone arm compared with 141 (55.3%) in the amiodarone arm (P < 0.001). In the primary efficacy endpoint, AF after electrical cardioversion occurred in 36.5% of patients in the dronedarone arm versus 24.3% of patients in the amiodarone arm, but patients receiving amiodarone presented a 20% increase in the predefined main safety endpoint (107 patients vs 83 patients) and tended to experience more premature drug discontinuation (34 patients vs 26 patients) than patients on dronedarone. When gastrointestinal side effects were excluded from the main safety endpoint (as predefined in the study protocol), there was a statistically significant decrease of 39% favoring dronedarone (61 patients vs 99 patients/P = 0.0021). Less bradycardia (8 patients vs 22 patients) and less pronounced QTc prolongation (27 patients vs 52 patients) were seen in the dronedarone arm than the amiodarone arm, and no torsade de pointes were reported in the study.

ATHENA showed that dronedarone significantly reduced mortality and cardiovascular hospitalizations. The primary outcome of first hospitalization due to cardiovascular events or death occurred in 31.9% of the dronedarone group compared with 39.4% in the placebo group (P < 0.001). A post-hoc analysis of data from the relatively small number of patients in ATHENA who remained in AF after treatment suggests that they may still have experienced improved outcomes with dronedarone and that the benefits of treatment were not therefore limited to patients who converted to sinus rhythm. Post-hoc analysis of ATHENA data has also provided evidence that there was a significant reduction in the risk of stroke in patients who were randomized to dronedarone (from 1.8% per year to 1.2% per year). This reduction was observed in patients treated or not with oral anticoagulants or antiplatelet drugs and was greater in patients with higher CHADS2 score. Furthermore, in a meta-analysis of 5 randomized controlled trials (DAFNE, EURIDIS, ADONIS, ERATO, and ATHENA) including 6,157 patients, reduced risk of cardiovascular hospitalization...
or death from any cause was demonstrated with dronedarone compared with placebo.42

It is of interest that in ATHENA, the occurrence of acute coronary syndromes (ACS) and stroke were also reduced with dronedarone.38 There are a number of possible explanations for this observation: for example, an unknown effect of dronedarone on vascular biology, the presence of AF as an arrhythmia might make a patient more at risk for an ACS event by as-yet unknown mechanisms (for example, a higher than usual heart rate), and an upstream cause of both AF and ACS. It is also important to note that in addition to its antiarrhythmic effect, dronedarone also lowers blood pressure, reduces heart rate and contractility, and is probably a coronary arterial vasodilator.35,36 However, the effects of dronedarone on structural atrial remodeling, neurohormonal activity, and inflammation have not been studied.

ANDROMEDA was a phase III, randomized study of dronedarone versus placebo in high risk patients with recently decompensated heart failure. It was designed to investigate whether dronedarone would reduce the rate of hospitalization due to heart failure and decrease mortality by attenuating the incidence of death due to arrhythmia.43 However, 7 months after the first patient was randomized the study was prematurely discontinued for safety reasons. During a median follow-up of 2 months a total of 37 patients, 25 in the dronedarone group (8.1%) and 12 in the placebo group (3.8%), died (hazard ratio in the dronedarone group, 2.13; 95% CI, 1.07 to 4.25; P = 0.03). The number of deaths attributable to arrhythmia or sudden death did not differ significantly between the 2 groups. Indeed, the excess mortality noted with dronedarone appeared to be predominantly related to worsening heart failure—10 deaths in the dronedarone group and 2 in the placebo group.43 Although these are small patient numbers and post-hoc subgroup analysis should be interpreted with caution, it may be that dronedarone is associated with worsening heart failure in high-risk patients with poor systolic function.43

How Does This New Evidence Have the Potential to Change Treatment Algorithms? Does New Evidence Suggest That Current Stratification Assessments for Therapy Should Be Changed?

Subsequent to the meeting, dronedarone has received approval from several regulatory authorities including the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMEA). The FDA label (but not the EMEA label) for dronedarone states that it is indicated “to reduce the risk of cardiovascular hospitalizations”—being the first antiarrhythmic agent to have a cardiovascular outcomes statement in its label. The potential impact of ATHENA and ANDROMEDA on the FDA label on treatment algorithms is discussed later, as is the possible place for dronedarone in the management algorithm.

Conclusions

Current antiarrhythmic drugs are useful for the treatment of AF but have limiting side effect profiles in many patient subgroups. A new antiarrhythmic drug should be able to demonstrate safety in randomized, controlled trials that include “hard” outcomes such as cardiovascular events and mortality. The new drugs that are in development appear to show promise. Ideally, a large database of experience, including control groups, would be established to confirm the safety of any new agent.

What Is the Newly Available Evidence on Catheter Ablation to Maintain Sinus Rhythm?

The ACC/AHA/ESC management guidelines for maintenance of sinus rhythm in patients with AF elevated catheter ablation to second-line therapy for all categories of patients, that is, those with no or minimal heart disease, hypertension with or without significant ventricular hypertrophy, coronary artery disease, and heart failure.6 Antiarrhythmic drugs were considered first line in all of the categories.

Since AF changes the electrical and structural properties of the atria, it is important to decide early in the course of the patient’s illness whether sinus rhythm is desired. Allowing patients to persist in AF for many years will cause irreversible damage to the atria and may prevent maintenance of long-term sinus rhythm.44 If a rhythm control strategy is selected, treatment of AF should commence at the first-detected episode and should be based on sinus rhythm restoration and aggressive treatment of associated conditions that promote atrial remodeling.44

Although relatively small in size, there have been several randomized prospective trials using radiofrequency catheter ablation versus antiarrhythmic drugs to maintain sinus rhythm.45 A meta-analysis of 6 trials demonstrated a reduced risk of AF recurrence by 65% at 1 year compared with antiarrhythmic medications.45 Furthermore, studies analyzing radiofrequency ablation for maintenance of sinus rhythm in patients with heart failure have shown both a substantial ability to maintain sinus rhythm and improvement in left ventricular function.46,47 Additionally, data in patients over 65 years old have also been published, reporting a good safety profile for ablation in older patients who were often excluded from earlier studies.48,49 However, the potential complications of performing catheter ablation for AF are important. Cappato and colleagues evaluated the prevalence and causes of fatal outcome in ablation patients and noted that death occurred in 1 of 1,000 patients.50 Furthermore, other serious complications occur in at least 1 to 2% of patients, including stroke, pulmonary vein stenosis, and cardiac perforation with or without tamponade. It is estimated that atrioesophageal fistula occurs in less than 1 in 1,000 patients but the true incidence is not clear.51

How Does This New Evidence Have the Potential to Change Treatment Algorithms?

While a considerable amount of new data have been published on the safety and efficacy of catheter ablation of AF since the 2006 ACC/AHA/ESC guidelines, what is needed to elevate ablation to a first-line status without controversy is a large randomized prospective trial of ablation versus antiarrhythmic drugs. The CABANA trial (NCT00578617) will hopefully address this need. However, although CABANA will provide a more solid basis for appropriate placement of ablation in the treatment algorithm for maintenance of sinus rhythm, there are substantial data that clearly show ablation to be a reasonable alternative to antiarrhythmic drugs at least in patients with no or minimal heart disease who have paroxysmal AF, assuming that the electrophysiologist performing the study has substantial experience in ablation. More data
are required to position ablation as a first-line alternative to antiarrhythmic drugs for patients who have persistent and long-standing persistent AF as well as in patients with significant heart disease.

**Does New Evidence Suggest That Current Risk Stratification for Rhythm Control Therapy Should Be Changed?**

When to choose catheter ablation for maintenance of sinus rhythm in patients with AF remains a major issue. The likelihood of benefit in reducing risk of stroke, prevention, or improvement in heart failure and left ventricular dysfunction, improvement in QoL, reduction in overall health costs, and reduction in mortality should be considered, but data from a major trial such as CABANA will be needed. The cost-effectiveness of radiofrequency catheter ablation compared with antiarrhythmic drug therapy for paroxysmal AF has been evaluated by Reynolds and colleagues. They concluded that in patients with drug refractory paroxysmal AF, ablation (with or without antiarrhythmic drug therapy) is a reasonably cost-effective therapy compared with antiarrhythmic drug treatment, based on improved QoL and avoidance of future health care costs.

Other studies have demonstrated improvement in left ventricular function and reduction in heart failure symptoms, and improvement in QoL. Whether the risk of stroke is reduced in patients who have a CHADS2 score of 2 or greater is still under study. Thus, at present ablation should not be offered as an alternative to long-term anticoagulant therapy in patients at high risk for stroke. Further, patients with few or mild symptoms are not the best candidates for ablation. It would seem that for certain subgroups of patients it is reasonable to consider ablation as first-line therapy. These might include young individuals who do not want to take a drug long term, those individuals in whom drug therapy is likely to result in the addition of a permanent pacemaker, and individuals in whom the only choice may be long-term amiodarone therapy that may have a greater risk to the patient than ablation.

Ablation of AF, even paroxysmal AF, demands a substantial degree of technical proficiency. In a well-experienced laboratory, where the operators have performed many AF ablation procedures, it may be reasonable to consider ablation for first-line treatment, even in patients who are more elderly and who have significant heart disease. This would clearly not be the case in less experienced laboratories. It has been suggested that national or even international guidelines should be established regarding competency to perform ablation of AF but no consensus has yet been reached.

**What Are the Barriers in Implementing Current Treatment Strategies?**

**Underdiagnosis of AF**

AF is most likely underdiagnosed, since up to 33% of patients with AF are asymptomatic. Asymptomatic episodes (on Holter/transtelephonic studies) are 10 to 12 times more frequent than symptomatic events, yet patients who are asymptomatic may still be at increased risk for stroke and mortality and may suffer from comorbidities such as heart failure, hypertension, and diabetes. Approximately 25% to 30% of patients presenting with strokes have previously undiagnosed AF.

Risk stratification could be used to select individuals for screening; this might involve, for example, showing patients how to take their pulse every day and reviewing the results on a monthly basis, continuous outpatient monitoring, or both. The level of understanding of AF among health care providers caring for higher-risk patients in hypertension, diabetes, and heart failure clinics requires further study.

**Recognition of AF as a Serious Condition**

Despite the availability of guidelines on AF management, AF is not always perceived as a serious health threat. Current management options focus on the relief of symptoms and short-term goals but do not address the risk of long-term outcomes such as morbidity, mortality, and cardiovascular hospitalization. A physician treating a patient for common comorbidities such as hypertension, heart failure, or diabetes may not view AF as an important problem. Patients may also think that AF is a benign condition and not be aware of the associated risk of stroke. This may be the result of misinformation or the lack of supporting educational/information materials that clearly explain the condition and its associated risks.

**Cost and Access to Treatment**

Although catheter ablation is being increasingly used to resolve AF and restore normal sinus rhythm in certain patient groups, the numbers of suitably equipped medical centers and trained personnel is inadequate even to accommodate these selected patient groups. This shortfall in resources occurs in developed countries, and in developing countries it is even greater. Given that there will always be patients who are not suitable for ablation therapy or prefer not to have it, there remains a need for safer and more effective antiarrhythmic drugs.

Costs and access to treatment vary from country to country, and in some areas there is no access to even basic assessment tools. For example, the populations of China, India, and Indonesia together represent approximately 50% of the total global population. In these countries, it may not be possible even to offer safe anticoagulation therapy to patients with AF because there is no infrastructure in place to enable patients to check regularly anticoagulation with INRs. In these countries different patient management systems must be developed. The cost effectiveness of catheter ablation, rhythm control, and rate control must be established based upon local health care delivery systems. This may vary considerably between developed and developing countries; therefore, treatment strategies and guidelines may vary from region to region.

**Barriers to Implementation of Guidelines**

Fragmentation of care has been cited as a major barrier to the effective implementation of current AF treatment guidelines. Even in developed countries, it is claimed that health care systems are not very well organized or integrated.

In the community, if a primary care physician does not understand that AF is a serious condition, the patient will be less likely to receive appropriate care. Until now many guidelines have been developed without consulting or involving primary care physicians. In the future, it will be important to involve
primary care physicians and internists in the guideline development process. In the UK, all stakeholders, including primary care physicians and pharmacists, are routinely involved with the development of guidelines that are produced by the National Institute for Health and Clinical Excellence (NICE). The NICE approach to the development of guidelines has generated some debate within other organizations about how the integrity of their future guidelines may be improved. It has been proposed that guidelines should be formulated by recognized methodologists who are free of conflicts of interest, rather than expert clinicians who are likely to have some conflicts of interest, which may be financial and/or intellectual.63

Physician and Patient Factors—Adherence to Treatment
(Patient Education Issues)

Physicians’ reluctance to prescribe warfarin, particularly in elderly patients, is often due to a perceived greater risk of bleeding, overestimation of the associated risks, underestimation of the stroke risk and clinical uncertainty or experience of warfarin.64

When the patient is prescribed medical therapy, their willingness to adhere to treatment frequently depends on effective patient education. Older patients may fear stroke more than death, and discussing “stroke risk” with patients is likely to elicit more awareness of the risks and need for treatment of AF. However, it should be considered whether it is necessary or desirable to create anxiety to emphasize the seriousness of AF or whether a preferred approach would be to offer patients the tools to manage and understand their condition. Effective patient education is also important, so that patients become more aware of whether or not they should ask to be referred for further treatment.

AF therapies are not always effective or may not be well tolerated. If currently available agents were more effective, easy to take, and with fewer side effects patients and physicians might be more positive about their inclusion in the treatment algorithm and might also be more proactive in helping patients adhere to treatment.

The materials that are currently available for patient education both nationally and internationally are not sufficient. Patients with AF may be in a demographic group that does not often use the Internet as a source of information. They may prefer to receive information from their physician and therefore need contact with a health care professional, who can provide them with appropriate support materials tailored to their educational needs. Other routes for delivery and exchange of information can include patient discussion groups and patient associations.

Conclusions

To combat the increasing burden of AF in the forthcoming decades it will be important to address all the components of the successful patient-care pathway, from patient identification and diagnosis, to management and treatment of patients throughout the disease progression. Quality educational and information materials must be available to assist with patient care so as to minimize the impact of this disease on the overall QoL and any potential reduction in life expectancy.

Should Treatment Strategies for AF Focus on Major Cardiovascular Outcomes Rather Than Control of Arrhythmia?

Impact of New Evidence on Treatment Strategies—Maintenance of Sinus Rhythm

A treatment algorithm for the maintenance of sinus rhythm was proposed in the 2006 ACC/AHA/ESC management guidelines for atrial fibrillation.6 The algorithm is based on consideration of safety first and efficacy next. In other words, all therapies listed have demonstrated success in maintaining sinus rhythm in various patients, but the order of selection of drugs or ablation was positioned according to safety profiles in certain patient subgroups rather than the degree of efficacy. Recognizing that AF may emerge along the cardiovascular continuum and may increase the risk of serious conditions such as heart failure (Fig. 1^3), the AF Exchange Group was asked to reevaluate the current treatment algorithm and suggest changes based on the recent approval of dronedarone in the United States. At the time of the meeting dronedarone had not received approval in Europe, so the discussion was directed at the US approval.

No or Minimal Heart Disease

Traditionally, flecainide, propafenone, and sotalol have been first-line therapies in patients without structural heart disease (Fig. 2). Data on dronedarone suggest it is safe and effective for patients in this category.35,36,65 The published guidelines position radiofrequency catheter ablation as second-line therapy in this group of patients. This was considered justifiable because it is reasonable to consider a more conservative initial treatment option for most patients in this group. However, some of the working group members felt catheter ablation could be considered as first-line therapy in these patients.

Hypertension

The published guidelines list hypertension with subcategories of patients with and without substantial left ventricular hypertrophy (LVH). This issue was discussed by the group and, since patients without substantial hypertrophy are treated by the same method as patients who have minimal to no heart disease, it was felt that this category could be simplified merely to state substantial LVH as the primary treatment category. The safety of dronedarone in such patients was discussed and most participants thought that there were enough safety data in such patients to elevate dronedarone as a first-line alternative to amiodarone. Ablation remains second-line therapy in this group. While propafenone and flecainide were not included in this category in the published guidelines, the participants suggested that the data to support this omission were not very robust. In essence, the concern is that patients with substantial ventricular hypertrophy will be more proarrhythmic with drugs that substantially slow conduction, and there are experimental models to support this, but in fact there are not many clinical studies that have evaluated this. Regardless, it was felt that until more safety data are known propafenone and flecainide should not be listed in this category. All agreed that sotalol and dofetilide were not safe agents to use in patients with substantial LVH.
Coronary Artery Disease

The participants agreed with the use of dofetilide and sotalol as first-line therapy in patients with a history of coronary disease. Based on the substantial number of patients with coronary artery disease represented in the various dronedarone clinical trials, the consensus was that dronedarone would also be a first-line therapy in this population.

Heart Failure

In the published guidelines, heart failure is not subcategorized by New York Heart Association classification I–IV. Only amiodarone and dofetilide had been shown to be safe in patients with significant heart failure and they were the ones listed as first-line therapy.

The participants considered the available data on the use of dronedarone in patients with heart failure. This issue is quite difficult since the only major safety concern with dronedarone treatment has been demonstrated in patients in the ANDROMEDA trial. This was a trial that compared dronedarone with placebo in patients who did not even require AF as an entry point but who had demonstrated recent acute decompensation from heart failure (NYHA III or IV) 1 month before admission. An increase in mortality in those receiving dronedarone resulted in early termination of this trial. However, in the ATHENA trial there were a substantial number of patients with milder forms of heart failure, for example class I and II, who did quite well without any increase in mortality. Thus, the participants considered all of these issues and decided it was more logical to subdivide heart failure into class I and II versus class III as noted in the proposed new scheme (see Fig. 2). Of note, there are few good data on the long-term use of any antiarrhythmic agent in class IV patients, and this was not considered in the new algorithm. In the new proposed algorithm, dronedarone along with amiodarone and dofetilide are listed for patients who have New York Heart Association class I and II failure, followed by catheter ablation as second-line therapy. For patients with class III heart failure, amiodarone and dofetilide are listed, but it was felt that more safety data were needed on dronedarone before it could be considered in this subgroup of patients.

Another vexing problem has been how to position any of these drugs in patients with diastolic heart failure. In most of the prospective trials evaluating antiarrhythmic drugs and heart failure, the numbers of patients with preserved left ventricular function and heart failure has not been well delineated and it is simply not clear on how safety of therapies in these patients compare with those who have left ventricular dysfunction. Thus, no further subcategorization was felt appropriate by the participants. It is evident that the comments of the AF Exchange Group correlate well with the current labeling for the United States. This is in contrast to the European labeling received subsequent to the meeting. Current labeling for the United States and Europe is summarized as follows:

- **United States**: MULTAQ is an antiarrhythmic drug indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent AF or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors (i.e., age > 70, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥ 50 mm or left ventricular ejection fraction [LVEF] < 40%), who are in sinus rhythm or who will be cardioverted.

- **EUROPE**: MULTAQ is indicated in adult clinically stable patients with a history of, or current nonpermanent AF to prevent the recurrence of AF or to lower ventricular rate.
How Can the Incidence of Thromboembolism and Stroke Be Reduced?

Existing and Emerging Risk Factors for Stroke in AF

AF is associated with a substantial risk of mortality and morbidity from stroke and thromboembolism, and strokes associated with AF are often more severe and more devastating than those linked to other cardiovascular conditions. The risk of stroke and thromboembolism in AF is closely associated with a range of comorbidities. Various clinical and echocardiographic features have been identified, although contemporary clinical risk stratification schemes for predicting stroke, transient ischemic attack (TIA), or thromboembolic events for patients with AF have not adequately assessed or systematically documented all the potential risk factors in the clinical trial populations.

The risk of stroke and thromboembolism in AF is not homogeneous, and various clinical and echocardiographic features have been identified to help to stratify the risk into high, intermediate, or low-risk categories. Four clinical features—prior stroke/TIA, advancing age, hypertension, and diabetes—are consistently identified as independent risk factors. Structural heart disease (left-ventricular dysfunction or hypertrophy) has recently been added to this list, which includes congestive heart failure, and there is increasing evidence that other factors should be considered in refining stroke and thromboembolism risk stratification for AF, for example, female gender. Vascular diseases including myocardial infarction, peripheral artery disease, and complex aortic plaque all increase thromboembolic risk in patients with AF, while the risk of stroke in AF increases with age, particularly over 75 years, and in those with impaired renal function (and proteinuria).

Other biological markers, such as plasma von Willebrand factor and fibrin D-dimer, have also been found to be risk factors for the development of stroke in AF but have not been adequately validated for use in clinical risk stratification.

It was felt that some of these variables, particularly common ones with the potential to have most impact, should be explored further with a view to possibly being included in stroke risk stratification assessments and that any new risk factors identified should be subjected to rigorous validation to ensure their effect is reproducible and robust. Echocardiography and other techniques should be used to look at the site of clot formation and that it might also be of value to investigate biomarkers of prothrombotic activity.

Risk Stratification Schemes and Treatment Guidelines

Current treatment guidelines recommend that vitamin K antagonists should be used for “high-risk” subjects and (usually) aspirin for “low-risk” subjects, but for “intermediate-risk,” many guidelines state “either warfarin or aspirin” can be used. This “either warfarin or aspirin” recommendation can cause uncertainty (or confusion) and may be used to justify a decision not to prescribe warfarin in “intermediate-risk” patients. The value of aspirin as a treatment option (with or without clopidogrel) has been questioned, as evidence of its protective benefit is minimal compared with warfarin and it is associated with significant bleeding risk.

In the primary care situation, there is a need for a simple risk stratification scheme that a physician can apply quickly and easily in the office. However, any risk stratification scheme that results in a large proportion of AF patients being categorized as “intermediate risk” will lead to uncertainty about the most appropriate choice of treatment, and it is also important to ensure that those classified as “low risk” are truly low risk, with no (or very low) risk of stroke and thromboembolism at follow-up. Schemes developed over the last 15 years for predicting risk of thromboembolism in nonvalvular AF are summarized in Table 1. These have modest ability to predict the risk of a thromboembolic event and several place a substantial proportion of patients in the “intermediate-risk” category (Fig. 3).

The CHADS 2 scoring system was felt to be the most simple and useful for assessment of when a patient has sufficiently high risk (CHADS 2 score of ≥ 2) to warrant anticoagulation. However, it placed 61.2% of patients in the intermediate category and many risk factors are not included. A novel schema (the CHA2DS2-V ASC score or “Birmingham 2009 schema”) incorporates additional risk factors, including vascular disease, female gender and age 65 to 74 years, and a comparison with existing schema showed a modest improvement in c-statistic over the CHADS 2 score, classified a small proportion into the “intermediate” risk category, hence allowing less uncertainty over whether a vitamin K antagonist or aspirin should be prescribed. Also, those in the “low-risk” category with CHA2DS2-V ASC were truly low risk with zero rate of thromboembolic events at 1 year.

| TABLE 1 |
| Schemes Developed for Predicting Risk of Thromboembolism in Nonvalvular AF |

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>All Patients</th>
<th>Subgroup*</th>
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<td>AFI</td>
<td>13.1</td>
<td>24.7</td>
<td>62.3</td>
<td>0.56</td>
<td>0.61</td>
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<td>SPAF</td>
<td>27.7</td>
<td>28.5</td>
<td>43.8</td>
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<td>Framingham</td>
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<td>16.4</td>
<td>0.62</td>
<td>0.69</td>
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<td>7th ACCP</td>
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<td>7.9</td>
<td>80.4</td>
<td>0.56</td>
<td>0.60</td>
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*Subgroup of 5,588 patients not on warfarin at baseline and with continuous follow-up off of warfarin for at least 12 months.

AFI – Atrial Fibrillation Investigators.

SPAF – Stroke Prevention in Atrial Fibrillation.

CHADS2 – Congestive Heart Failure, Hypertension, Age ≥75 years, Diabetes Mellitus and prior Stroke or Transient Ischemic Attack.

Framingham Score.

ACCP 2008 – American College of Chest Physicians.
in contrast to the subjects classified as “low risk” using the CHADS2 schema (i.e., a score = 0) who still had an annual event rate of 1.4%/year.

Once we can adequately identify truly low-risk subjects (CHA2DS2-VASc score = 0), who probably do not need antithrombotic therapy, all others (CHA2DS2-VASc score ≥ 1) can be managed with oral anticoagulation, especially with the new oral anticoagulant agents (e.g., dabigatran) that would overcome the inherent limitations of the vitamin K antagonists. Such a simplified approach would help in our management of such patients.

**Poor Implementation of Treatment Guidelines**

The vitamin K antagonists have a narrow therapeutic window of efficacy and safety, and frequent monitoring is required. There is wide variability in dose response and numerous food and drug interactions. In addition, the delayed onset of action means that in some cases it may be necessary to initiate anticoagulation with either heparin or a low molecular weight heparin until the INR reaches a therapeutic level. In clinical practice, efficacy is compromised by inadequate dosing and poor compliance, and these agents are among the most common classes of drugs implicated in adverse events. Poor compliance is compounded by uncertainty among physicians about how to apply the guidelines; there are problems associated with the content and format of the guidelines, and preconceived views and biases of patients and physicians also affect their implementation.

**Emerging Treatment Options for Stroke Prevention in AF**

Outcomes trials are essential to assess the benefit of new anticoagulant drugs, and many are currently being investigated in clinical trials. These agents fall broadly within 2 categories, oral direct thrombin inhibitors and oral factor Xa inhibitors (Fig. 4). It is hoped that these new drugs will overcome some of the limitations of the vitamin K antagonists.

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**Figure 3.** Comparison of risk stratification schemes to predict thromboembolism in non-valvular AF. AFI – Atrial Fibrillation Investigators. SPAF – Stroke Prevention in Atrial Fibrillation. CHADS2 – Congestive Heart Failure, Hypertension, Age ≥75 years, Diabetes Mellitus and prior Stroke or Transient Ischemic Attack. Framingham Score. ACCP 2008 – American College of Chest Physicians.

**Figure 4.** Novel anticoagulants.
in terms of allowing fixed dosing, fewer food and drug interactions, lack of requirement for regular monitoring, and avoidance of the variability of anticoagulation intensity with its associated resulting risk of stroke and bleeding. The agents that are at the most advanced stages in clinical trials are listed in Table 2.

Dabigatran is a novel, direct thrombin inhibitor that is given orally as the prodrug dabigatran etexilate. RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy, Warfarin, Compared to Dabigatran) was the largest AF outcomes study ever carried out (18,113 patients in 40 countries) and has set the standard in terms of outcomes trials. Results from the RE-LY trial demonstrated that in patients with AF and a risk of stroke, dabigatran etexilate was associated with lower rates of stroke and systemic embolism but similar rates of major hemorrhage compared with adjusted-dose warfarin.60

Two doses of dabigatran (150 mg and 110 mg bid) were studied. Compared with warfarin treatment, dabigatran 150 mg bid reduced the rate of stroke and systemic embolism by 27%, but 110 mg bid did not reduce the rates.80 Both doses substantially reduced hemorrhagic stroke compared with warfarin, which may in part be due to the unstable INR with warfarin. The most severe strokes (fatal or disabling) were reduced by 34% with the 150 mg dose. A slightly higher rate of MI was observed with both doses compared with warfarin; as the effect does not appear to be dose related, it may be due to the absence of warfarin rather than the presence of dabigatran. The only adverse effect more common with dabigatran than with warfarin was dyspepsia, but no differences in serum transaminases were found among groups.

The group considered how one might position the use of either dose of dabigatran. It was universally agreed that treatment with 150 mg bid would be considered for a patient with a CHADS2 score of 3, who required anticoagulant therapy. However, there were mixed views about the value of a 110 mg bid dose. Some felt that only the 150 mg dose should be marketed in order to keep treatment options as simple as possible. There was general agreement that it would be a difficult decision to switch a patient from warfarin to dabigatran if they had “rock stable” INRs and no tolerability issues, and it was suggested that the 110 mg dose might be of little value in a patient who would otherwise have received warfarin. The majority view was that it would be desirable to have a choice of 2 doses so that the lower dose could be given to patients who have a higher risk of bleeding—assessed using factors such as age, propensity to fall, and prior history of bleeding—or to patients with poor renal function or who were taking certain concomitant medications.

Table 2

<table>
<thead>
<tr>
<th>Medication</th>
<th>Action</th>
<th>Phase III Trial</th>
<th>Comparator</th>
<th>Design</th>
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<td>RE-LY</td>
<td>Warfarin</td>
<td>Noninferiority</td>
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<td>Apixaban</td>
<td>Anti Xa</td>
<td>AVERROES</td>
<td>Aspirin</td>
<td>Superiority</td>
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<tr>
<td>Rivaroxaban</td>
<td>Anti Xa</td>
<td>ARISTOLE</td>
<td>Warfarin</td>
<td>Noninferiority</td>
<td>15,000</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Anti Xa</td>
<td>ROCKET-AF</td>
<td>Warfarin</td>
<td>Noninferiority</td>
<td>14,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ENGAGE</td>
<td>Warfarin</td>
<td>Noninferiority</td>
<td>16,500</td>
</tr>
</tbody>
</table>

An important safety issue that needs to be addressed is what can be given as an antidote in case of hemorrhage or a need for emergency surgery in a patient who is receiving dabigatran? Cost-effectiveness data will also be required to justify the use of a new agent with a higher acquisition cost than warfarin; good cost data are available for dabigatran and the reduction in risk of stroke and reduced monitoring requirements will help to build a strong cost-effectiveness case for this drug. Finally, in a patient with both AF and coronary artery disease, the beneficial effect of warfarin on myocardial infarction will need to be weighed against reduction in stroke with dabigatran.

Future Perspectives

The focus of the management of AF may be changing—from alleviating symptoms to improving “hard” outcomes. In the future, we may see AF outcomes trials involving multiple treatment approaches, including rhythm control and thrombosis management. Such trials are awaited with interest.

References


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Professor Gunter Breithardt attended the meeting representing the World Heart Federation.


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