Atrial fibrillation: Challenges and opportunities

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Atrial fibrillation (AF) is the most common sustained arrhythmia encountered in clinical practice. There are many pharmacological and nonpharmacological options available for AF patients. There is, however, a great deal of dissatisfaction with the available treatments of this arrhythmia. Furthermore, AF management remains associated with many challenges that make the treatment of AF a vexing problem. The present overview discusses these challenges and explores the opportunities associated with them.

Key Words: Anticoagulation; Arrhythmia management; Atrial fibrillation; Epidemiology; Treatment

Atrial fibrillation (AF) is the most common sustained arrhythmia treated by physicians today. Despite decades of investigation and experience with the treatment of AF, many challenges remain. Contemporary challenges include the following examples: an incomplete understanding of the pathophysiology of AF; an increasing prevalence of AF; a lack of efficacy of and the presence of adverse effects from antiarrhythmic drug therapy; and suboptimal use of antithrombotic therapy for the prevention of stroke and thromboembolism. On the other hand, each of these challenges is associated with a number of opportunities for improved understanding and management of this vexing problem. The present overview will explore each of the challenges in the management of AF listed above and some of the opportunities associated with them.

CHALLENGE – INCOMPLETE UNDERSTANDING OF THE PATHOPHYSIOLOGY OF AF

The role of individual components of the pathophysiology of AF – both overall and in individual instances – remains unclear at this time. It is unlikely that a single pathophysiology is operative in all or even the majority of cases. Insight into the pathophysiology of AF, particularly if it could be determined at the bedside, would help in the formulation of a rational, rather than the current empirical, approach to therapy. Figure 1 presents a schematic outline of the paradigm used to summarize our current understanding of the pathophysiology of AF (1). The key elements of this paradigm are triggers, substrate, re-entry, remodelling and modulating factors. These elements have been included in the paradigm for understanding the pathophysiology

Fibrillation auriculaire : Défis et possibilités

La fibrillation auriculaire (FA) est l'arythmie la plus fréquemment rencontrée en pratique clinique. Plusieurs options pharmacologiques et non pharmacologiques sont offertes aux patients qui en souffrent. On note en revanche une profonde insatisfaction à l'égard des traitements administrés pour cette arythmie. De plus, le traitement de la FA reste associé à de nombreux défis et demeure un problème épineux. La présente synthèse fait le point sur les obstacles rencontrés dans ce domaine et explore différentes manières de contourner chacun.

of all tachyarrhythmias for more than 20 years. In the specific case of AF, the importance of remodelling has only become apparent in the past decade. The recognition of the large number of modulating factors for this particular tachyarrhythmia is also relatively recent (1). It is not the intention of the present article to review or discuss in detail the pathophysiology of AF, or the number and nature of modulating factors – this information can be found elsewhere (1). Instead, it is our intention to point out that the first challenge with respect to AF is our incomplete understanding of its pathophysiology. Nevertheless, there are opportunities in the area of the pathophysiology of AF, as outlined in Table 1.

OPPORTUNITIES – INCOMPLETE UNDERSTANDING OF THE PATHOPHYSIOLOGY OF AF

Exploitation of modulating factors (eg, inflammation and C-reactive protein)

It has been known for some time that inflammation, for which C-reactive protein (CRP) is a marker, is a factor in the pathophysiology of AF in the setting of recent cardiac surgery (2). However, inflammation (and CRP as a marker of inflammation) in AF has been increasingly recognized (3-5), and has been recently reviewed (6). Serum CRP appears to be a significant independent predictor of the risk of AF. Furthermore, the favourable effect of the use of anti-inflammatory glucocorticoid therapy as part of the treatment for the prevention of recurrent AF illustrates the point that the treatment of modulating factors, when they are recognized, should be a part of the

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Figure 1) Schematic diagram illustrating the current paradigm for understanding the pathophysiology of atrial fibrillation. Reproduced with permission from reference 1

management of individual cases of AF (5). Although most physicians would be reluctant to recommend the widespread use of glucocorticoid therapy for patients with AF, statins have similar properties, and nonrandomized observational studies have suggested that this class of drug may have a beneficial effect in the management of AF (7,8). Many other examples could be cited here, including the treatment of hyperthyroidism, sleep apnea and modulating factors that stretch the atria (eg, hypertension, valvular heart disease and congestive heart failure). The principle, however, is clear.

Exploitation of structural remodelling – Fibrosis is a key

Remodelling of the atria is an important part of the pathophysiology of AF and has three main components: structural, electrical and mechanical (1). The key factor in structural remodelling is fibrosis, which, unlike electrical remodelling, is not readily reversible. It is, however, preventable – as has been demonstrated in animal model experiments in the laboratory of Dr Stanley Nattel at the Montreal Heart Institute (Montreal, Quebec) using enalapril (9) and by others using candesartan (10). These observations are the foundation for several clinical reports examining the role of such drugs in the prevention of AF. For example, the Montreal Heart Institute reported their experience in the Studies Of Left Ventricular Dysfunction (SOLVD) trial (11), in which the drug enalapril reduced the development of AF compared with placebo treatment. There are reports of similar results with other angiotensin-converting enzyme inhibitors and angiotensin receptor blockers compared with placebo or with other classes of drugs; these reports arise from post hoc analyses of other randomized and nonrandomized studies of patients with congestive heart failure and hypertension (12-14). This subject has also been recently reviewed (6,15). A beneficial effect of these drugs with respect to AF has not been universally found, and it is not yet clear whether the effect is specific to certain drugs or to certain types of patients. A positive effect of angiotensin-converting enzyme inhibitors and angiotensin

TABLE 1
Opportunities with respect to incomplete understanding of the pathophysiology of atrial fibrillation

- More studies on the pathophysiology of atrial fibrillation are needed
- Better utilization of what we already know
- Exploitation of modulating factors, and structural and electrical remodelling
- Development and use of 'nonantiarrhythmic' drug therapies
- Understanding and exploitation of genetic factors

receptor blockers does seem to be more evident when 'more diseased' patients, such as those with poor ventricular function or hypertension with left ventricular hypertrophy, are studied.

Exploitation of electrical remodelling (eg, role in immediate/early recurrence of AF after electrical cardioversion)

Another important aspect of atrial remodelling is electrical remodelling. Although the work of Allessie's group (16) has been more widely recognized and cited, the observation of the hallmark of electrical remodelling – namely, shortening of the atrial effective refractory period – was almost simultaneously made in a Canadian study originating from the University of Western Ontario (London, Ontario) (17). Electrical remodelling has clinical relevance that is often underappreciated (eg, immediate or early recurrence of AF [IRAF/ERAF] occurring after electrical cardioversion) (18). The probability of IRAF/ERAF after electrical cardioversion is related to the duration of the AF and is more likely to occur when AF has been present for less than 30 days (19). This time period coincides with and is likely the result of reversible electrical remodelling. Electrical remodelling of atrial myocytes includes calcium loading and the downregulation of calcium channels. Much of this work originated in the laboratory of Dr Stanley Nattel at the Montreal Heart Institute, and he has recently reviewed this topic (20). Several studies have shown that the addition of drugs that block calcium entry into myocytes, such as verapamil or irbesartan, to an antiarrhythmic drug, even for short periods around the time of electrical cardioversion, can have a remarkable effect in preventing IRAF/ERAF (21-23). There are probably additional ways in which electrical remodelling and its counterpart, reverse remodelling, can be exploited. For example, a recent study has shown that reverse remodelling can restore the sensitivity of AF to pharmacological cardioversion after sinus rhythm is present for at least four days before AF recurs (24). More work on the clinical applications of these observations is needed.

Understanding and exploitation of genetic factors

The role of genetic factors in the pathophysiology of AF, as well as the possibilities for their exploitation, is not yet understood. There certainly are familial forms of AF (25), but in general, these patients are younger than most other patients with AF. The degree to which genetic factors play a role in the more common forms of AF is uncertain, but it is likely important. A genetic basis for the greater prevalence of AF observed in men has recently been proposed (26). It remains to be seen whether genetic differences can be exploited, for example, by the utilization of pharmacological therapies that are more likely to be successful in an individual patient (pharmacogenetics).

CHALLENGE – INCREASING PREVALENCE OF AF

Much is known about the epidemiology of AF. Its prevalence is greater in older subjects and in men of all age groups (27,28). The prevalence of AF ranges from 0.1% among adults younger than 55 years of age to 9% in those older than 80 years of age. The overall prevalence in men is 1.1% and in women is 0.8% (27). The lifetime risk of developing AF between 40 and 95 years of age is 26% for men and 23% for women (28). This lifetime risk does not change substantially with increasing age because, although life expectancy decreases with age, AF incidence increases with age. The most common coincident cardiovascular diagnosis in patients with AF is hypertension (28). Although the prevalence of congestive heart failure is less common among those with AF than among those with hypertension, the prevalence of AF is much higher among those with congestive heart failure than among those with hypertension (29). For a variety of reasons, including aging of the population, the prevalence of AF in the population is increasing. It is estimated that 2.3 million adults in the United States currently have AF and that this number will increase to close to six million by the year 2050, with more than 50% of those affected being older than 80 years of age (28). Opportunities with respect to the increasing prevalence of AF are discussed below (Table 2).

OPPORTUNITIES – INCREASING PREVALENCE OF AF

Exploitation of opportunities for primary prevention – Targets are congestive heart failure/poor left ventricular function and hypertension

In the face of these epidemiological features, the clearest need is to augment efforts at primary prevention. The target groups for primary prevention of AF include those with hypertension or congestive heart failure and, to a lesser degree, those with coronary artery disease. The value of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and statins have already been mentioned in the preceding sections, and these drugs should be used whenever there is an established indication for them with the added potential benefit of AF prevention. Recent evidence suggests a similar advantage for carvedilol in patients with congestive heart failure (30). Moreover, the use of atrial-based pacing when there is an indication for a pacemaker or cardioverter-defibrillator should also be considered when the prevention of AF is a goal (31).

New management strategies (eg, nurse clinician AF clinics)

The large and increasing number of patients with AF, and the need to frequently adjust their treatment (eg, anticoagulation, antiarrhythmic drugs and rate control drugs) has, or soon will, overwhelm the standard care system. Furthermore, these patients need substantial education about their condition and its treatment. Finally, some of these patients will be considered for newer innovative therapies such as catheter ablation and implantable devices. A similar condition involving patients with pacemakers and cardioverter-defibrillators led to the development of nurse clinician clinics, which work with physicians in a team approach. Similar clinics could be established for AF patients and could also include other members, such as pharmacists and dietitians.

TABLE 2
Opportunities with respect to the increasing prevalence of atrial fibrillation (AF)

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- Primary prevention of AF
 - The targets are congestive heart failure/poor left ventricular function and hypertension
 - New management strategies
 - For example, nurse clinician AF clinics
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CHALLENGE – INEFFECTICACY AND ADVERSE EFFECTS OF ANTIARRHYTHMIC DRUGS

Current antiarrhythmic drugs are plagued by significant side effects and a relative lack of effectiveness. The most effective drug for the maintenance of sinus rhythm in AF patients is amiodarone, which is well known to have a significant number of adverse effects. One of the most widely quoted studies illustrating the superiority of amiodarone in this setting was led out of the Montreal Heart Institute (Canadian Trial of Atrial Fibrillation [CTAF]) (32). In that trial, amiodarone was shown to reduce recurrent AF compared with other first-line medical treatment strategies (sotalol and propafenone). However, a large number of patients on amiodarone had recurrences of AF, and amiodarone tended to have more adverse effects, which lead to discontinuation of the drug, and thus, limited its overall effectiveness. Similar results were also recently reported in the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) (33), which compared amiodarone, sotalol and placebo in patients with persistent AF. A time-dependent covariate analysis in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial demonstrated that antiarrhythmic drug therapy for AF is associated with increased mortality after controlling for the presence of sinus rhythm (34). One potential explanation for this observation is that the beneficial effect of these drugs in maintaining sinus rhythm is offset by their adverse effects. These offsetting effects would be obscured in an overall analysis. Importantly, in the case of the AFFIRM trial (35), in which a high proportion of patients were treated with amiodarone, the excess mortality appears to be noncardiovascular. The inefficacy of drugs for the maintenance of sinus rhythm was recently reviewed (36). Opportunities with respect to the inefficacy and adverse effects of antiarrhythmic drugs are discussed below (Table 3).

OPPORTUNITIES – INEFFECTICACY AND ADVERSE EFFECTS OF ANTIARRHYTHMIC DRUGS

New strategies (eg, intermittent therapy)

Intermittent antiarrhythmic drug therapy, sometimes referred to as the 'pill-in-the-pocket' approach, is a concept that has been around for some time but has not yet been widely adopted. The basis for this approach is pharmacological cardioversion, which has been recently reviewed and, in general, works best when the drug is administered shortly after the onset of AF (37). With the pill-in-the-pocket approach, patients are provided with an antiarrhythmic drug and instructed to take it whenever they recognize a symptomatic episode of AF. Until recently, studies of pharmacological cardioversion were performed with continuous electrocardiographic monitoring. In a recent study, patients were successfully treated in the emergency department with a single dosage of flecainide or propafenone, and were then followed as outpatients (38).

TABLE 3
Opportunities with respect to inefficacy and adverse effects of antiarrhythmic drugs

- New strategies
 - For example, intermittent therapy; target is recent onset paroxysmal atrial fibrillation
- Rate control as a primary therapy for selected patients
 - Target is elderly patients with persistent atrial fibrillation
- Refinement and use of nonpharmacological therapies
 - Role of catheter ablation and devices remains to be defined
- Continued search for better and safer antiarrhythmic drugs

Patients with recurrences of AF (n=165) were instructed to take their drug 5 min after the onset of symptomatic AF. Self-administered outpatient oral therapy interrupted AF in 92% of 618 episodes, markedly reducing emergency room visits and hospitalizations. One potential serious adverse effect of this strategy is the development of atrial flutter with 1:1 conduction, which occurred in one patient.

Rate control as a primary therapy for selected patients

Seven randomized trials comparing strategies of rate- versus rhythm-control for the management of AF have been published to date and two more are in progress. These studies were recently reviewed (39). Historically, the rate-control approach came first. However, with the advent of more effective antiarrhythmic medications and electrical cardioversion, the rhythm-control approach soon became more popular among physicians, based on the presumed benefits of the rhythm-control approach. Nevertheless, the presumed benefits of the rhythm-control approach, at least using current antiarrhythmic drugs, have not been realized (39). Currently, the rate-control approach may be considered primary therapy for patients similar to those enrolled in the trials – elderly patients with persistent AF and stroke risk factors (40). Given that one-half of patients in the United States with AF are older than 75 years of age (41), the rate-control approach is a good initial approach for many patients. The only apparent reasons for using the rhythm-control approach in such elderly patients is failure of the rate-control approach to control symptoms or informed patient preference. Notably, patients with congestive heart failure and younger patients with paroxysmal AF were under-represented in these trials.

Refinement and the use of nonpharmacological therapies

Nonpharmacological therapies for the management of AF, such as catheter ablation, have recently undergone tremendous refinement and provide an important strategy for managing AF, often providing definitive management in patients who have failed antiarrhythmic drug therapy. It is now known that the important sites for ectopic foci that trigger AF are often near the junction of the atria and the thoracic veins, particularly the junction of the left atrium and the pulmonary veins (42). Early procedures were aimed at the destruction of ectopic foci within the pulmonary veins; however, these procedures were often associated with subsequent pulmonary vein stenosis. Thereafter, the goal of ablation was to electrically isolate the pulmonary veins within the left atrium. The latter procedure provided good results in those with paroxysmal AF. Other procedures, such as wide area circumferential ablation around the pulmonary veins,

have also been used (43). Denervation by ablating in the vicinity of autonomic ganglia located in the fat pad of the atrio-ventricular groove may be important in some patients (44). Another approach includes ablation in atrial areas with complex fibrillatory atrial activity (45). Emerging evidence suggests that if these procedures are to be applied with success in persistent or permanent AF, additional ablation in both the left and right atria are likely required. Repeat procedures are often necessary (30% of patients or more) to achieve success. Success itself has been variously defined and a number of patients continue to have asymptomatic AF (46). The learning curve for AF ablation is shallow and long-term results have not been reported from enough robust, long-term, follow-up studies to know whether early results are durable (47). Complications from these procedures are not inconsequential and are partly due to the long procedure duration and to the need for aggressive antithrombotic therapy during the procedure; complications include cardiac tamponade, stroke, phrenic nerve damage, pulmonary vein stenosis and others (47). Left atrial to esophageal fistula is a rare but feared complication because of its high fatality rate (48). Given these factors and the lack of randomized clinical trials using clinically important end points that compare this form of therapy with more traditional therapy, the exact role of ablation for the treatment of AF remains undefined. Similarly, the role of implantable devices for therapy of AF also remains undefined (49). While research regarding these nonpharmacological approaches to AF therapy continue, so does the search for newer and better antiarrhythmic drugs (50).

CHALLENGES: SUBOPTIMAL USAGE OF ANTITHROMBOTIC THERAPY

Antithrombotic therapy is an important part of the therapy for AF. The need for antithrombotic therapy is individualized by the presence or absence of stroke risk factors. A number of schemes have been promoted for this purpose and, while they are generally similar, there are differences (51). Accordingly, there is uncertainty among physicians regarding the need for anticoagulation of some AF patients. The underutilization of vitamin K antagonists has been emphasized (52). Furthermore, the recently published Euro Heart Survey on Atrial Fibrillation (53) showed that although 67% of eligible patients received anticoagulation therapy, 49% of ineligible patients received oral anticoagulation therapy. Thus, not only are patients who need anticoagulation undertreated, patients who do not need it are overtreated. Furthermore, the data on which risk stratification was based are now nearly two decades old, and the importance of well-treated hypertension as a risk factor, for example, is questioned. Finally, the risk and complexity of using vitamin K antagonists is well known by all physicians (54). Opportunities with respect to the suboptimal usage of antithrombotic therapy are discussed below (Table 4).

OPPORTUNITIES – SUBOPTIMAL USAGE OF ANTITHROMBOTIC THERAPY

Refinement and improvement of risk stratification for stroke/thromboembolism

The Atrial Fibrillation Investigators (AFI) systematically pooled data from five trials of anticoagulation therapy in patients with AF (55). This analysis demonstrated that several risk factors are associated with a risk of stroke of more than 5% per year without warfarin therapy. Patients with none of these

risk factors had a low risk of stroke of less than 1% per year without warfarin. For example, age was shown to increase the risk of stroke by a factor of 1.4 per decade. These investigators published a simple table to express the relationship of age with the following other stroke risk factors: a history of hypertension; a history of diabetes; and a history of previous stroke or transient ischemic attack (TIA). Another risk stratification scheme differed slightly, identifying women 75 years or older, hypertension, history of stroke or TIA, and impaired left ventricular function as clinical risk factors for stroke (56). Still, other schemes include echocardiographic characteristics. In general, we favour schemes that recognize a continuum of risk rather than a simple dichotomy of 'low' and 'high' risk, that are simple and useful at the bedside, and that do not require tests such as an echocardiogram. The recently proposed CHADS₂ (Congestive heart failure, Hypertension, Age, Diabetes, Stroke/TIA) risk assessment meets these criteria (57). CHADS₂ incorporates features from both the Stroke Prevention in Atrial Fibrillation (SPAF) trial and AFI, and was validated in a population of 1733 Medicare beneficiaries with nonvalvular AF who were not receiving warfarin at hospital discharge. There is a need to examine more contemporary databases to devise a scheme that more readily identifies high-risk patients and to consolidate the existing schemes in a way that facilitates understanding and fosters the appropriate use of antithrombotic therapy.

Development of new and better alternatives to vitamin K antagonists

Vitamin K antagonists can be very difficult drugs to use (54). Accordingly, there has been much interest in the evaluation of other or newer antithrombotic therapies. Thus far, there are no other satisfactory alternatives. Recent hopes were pinned on the oral antithrombin drug ximelagatran. Ximelagatran is

TABLE 4
Opportunities with respect to suboptimal usage of antithrombotic therapy

- Refinement and improvement of risk stratification for stroke and thromboembolism
- Development of new and better alternatives to vitamin K antagonists

an orally administered direct thrombin inhibitor that prevents the conversion of fibrinogen to fibrin by thrombin. The results of two large trials using this drug in patients with AF (58,59) showed similar efficacy to that of warfarin but also identified a potential for unexpected liver toxicity. Accordingly, the drug has not yet been approved for the indication of thromboembolism prophylaxis in AF. Two other trials assessing the alternative therapies idraparinux and acetylsalicylic acid plus clopidogrel have recently been terminated for excessive bleeding in the case of the former, and a lack of efficacy in the case of the latter when compared with vitamin K antagonists. Nonpharmacological therapies for this indication are also being explored but are at a very early stage of development. Finding suitable alternatives to vitamin K antagonists for thromboembolism prophylaxis in patients with AF remains an unmet need and a future opportunity.

THE FUTURE

The management of AF has become increasingly complex in recent years. In optimizing therapy for each patient, the physician is faced with many decisions on a day-to-day basis. The challenges are numerous and daunting; however, each challenge also presents a number of opportunities. Seizing these opportunities over the next few years will lead to improved management of this vexing clinical problem.

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