Atrial Fibrillation: A Perspective
Thinking Inside and Outside the Box

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Atrial fibrillation (AF) is a common clinical problem that is increasing in prevalence and is inextricably linked to another burgeoning cardiovascular problem, namely, congestive heart failure. There is increasing evidence that AF, at least in some population subsets, may be part of a spectrum of atherosclerotic vascular disease, hypertension, inflammation, diastolic dysfunction, and the metabolic syndromes. AF is part of a family of atrial tachyarrhythmias (Figure 1). A panel of experts has recently characterized the definition and position of AF within this group of tachyarrhythmias. Nonetheless, this family of tachyarrhythmias is closely interrelated, and the individual tachyarrhythmias often coexist in the same patient. Although the present discussion focuses on AF, many of the points made with regard to AF apply to these other tachyarrhythmias to varying degrees.

Recently, international panels of experts have also created clinical practice guidelines and perspectives on future research directions for AF. These documents are a rich source of reference to the vast literature on AF. It is not the intention of the present article to review this literature, and, in particular, it is not intended that the reader will use the present article as a manual for managing AF. However, the perspective is intended to provide a framework for rational thinking about the management of AF.

Inside the Basic Scientist’s Box

A schema of how a basic scientist might currently view AF is presented in Figure 2. In this schema, modulating factors surround the basic elements of arrhythmogenesis, and the focus is on the mechanisms for initiation and perpetuation of AF. In this particular paradigm, a trigger and substrate interact to form a reentrant circuit or circuits, but provision is also provided for a trigger to lead directly to AF. The consequences of the interaction between triggers and substrate are dependent in part on the milieu created by multiple modulating factors and in particular the autonomic nervous system. The relative influence of these pathways in the pathogenesis of AF has always been controversial, and their deemed importance has waxed and waned over the years. Until recently, reentry based on the multiple wavelet hypothesis, attributed to Moe and Abildskov, has held predominance, partly because of the mapping experiments of Allessie and colleagues. However, the multiple wavelet hypothesis was preceded by hypotheses that invoked single or multiple rapidly firing foci and other reentry concepts (see Waldo for a review). Recent observations on the initiation of AF from the area of the pulmonary veins and the concepts of fibrillatory conduction and of rotors have rekindled consideration of some of the older concepts, presented some new options, and lessened the dominance of the multiple wavelet hypothesis. However, the relative roles of abnormal automaticity and reentry in the pulmonary vein region for initiation and perpetuation, respectively, of AF are entirely unclear at the present time. Furthermore, it is not clear to what extent the competing concepts are substantially different and to what extent they overlap with the use of different terminology.

In addition, a better understanding of a number of processes collectively referred to as atrial remodeling has added to the complexity of the pathophysiology of AF. Remodeling is included in the schema in Figure 2 and outlines further subdivision of atrial remodeling into electric remodeling, contractile remodeling, and structural remodeling. One of the main reasons for making a distinction among types of remodeling is that the first 2 types of remodeling seem to be reversible, whereas the last is less so, and this probably has important implications for therapy. Another aspect of the schema in Figure 2 is the ubiquitous presence of a number of modulating factors that may contribute to development of AF, may help to perpetuate it, or may develop as a result of AF. In this model, these factors may act as risk “factors” for the development of AF, but in the clinical setting, AF may actually be a risk “marker” (see below).

As mentioned, modulating factors can be either those that help to initiate and maintain AF (enabling) or those that complicate AF. Some of these are depicted in Figure 3. A good example of an enabling factor is C-reactive protein, most clearly in the case of AF associated with recent heart surgery but also in a more general sense. On the other hand, coagulation factors contributing to the propensity for thromboembolic complications like stroke are an example of complicating factors.

Despite the fact that this type of construct has facilitated basic research and offers our best hope for breakthroughs in understanding of pathophysiology leading to new and effec-
tive therapies, it is not useful at the bedside. Two problems with the schema are (1) that it focuses entirely on AF itself and (2) that in any individual case we do not know which parts of the process are critical and vulnerable to treatment. As depicted in Figure 2, the points of potential intervention are numerous. Focusing on AF itself has its limitations because the extent to which AF is either a cause of or a consequence of other vascular conditions predisposing to stroke and congestive heart failure is incompletely understood at this time. Finally, the schema in Figure 2 does not readily allow one to incorporate a number of clinical observations about the epidemiology and clinical pathophysiology of AF.

Inside the Clinician’s Box
Figure 4 represents a simpler schema that borrows heavily from the basic science perspective and begins to integrate some of the clinical knowledge base, although it is certainly incomplete in the latter respect. A group of basic and clinical experts has recently brought together some of the perspectives of the 2 viewpoints, basic and clinical science, in a review,15 but more effort will be needed to integrate these concepts into clinically useful schemas.

Figure 2. The basic scientist’s box. A substrate and trigger are the basic elements for mechanisms that invoke reentry. However, the model also provides for a rapidly firing focus (trigger) to lead directly to AF via fibrillatory conduction. It is not always possible in current models to distinguish between a rapidly firing focus and a single, small reentrant circuit. AF itself leads to remodeling that tends to perpetuate the process. Modulating factors contribute to AF initiation and perpetuation, and AF can produce modulating factors that further perpetuate it or produce manifestations of AF.

Figure 3. Schema illustrates some of the numerous modulating factors for AF. Both Figure 2 and Figure 4 depict the role of modulating factors in the pathogenesis of AF; these are discussed in the text. ANS indicates autonomic nervous system; PV, pulmonary vein; and LV, left ventricular.

Figure 4 recognizes that with the use of a time-based clinical classification of AF, there are 3 basic types of recurrent AF: paroxysmal, persistent, and permanent.6 The number of potential intervention points is consolidated in the schema in Figure 4, and it starts to have some relevance at the bedside. In this schema, paroxysmal AF (AF that starts and stops by itself) is dominated by the “trigger” concept. The concept of modulating factors (Figure 3) and “triggers” is broader in the clinical setting than from the basic science perspective. A broader definition of “triggers” that includes bradycardia allows one to rationally incorporate other modes of therapy such as pacing.16 It is precisely because substrate is less capable of maintaining AF that the tachyarrhythmia stops in the paroxysmal form of AF. In this type of AF, it should be expected that therapy aimed primarily at the trigger would be efficacious in a large number of instances. The observation that simple pulmonary vein isolation is more effective in paroxysmal AF than it is in persistent AF17 would fit with such a concept. Studies of recent-onset AF often demonstrate a high rate of spontaneous cardioversion in the placebo group.18 Recent-onset AF is vulnerable to pharmacological cardioversion, whereas persistent AF is less so.4 These observations may be further evidence of how the differential vulnerability of substrate and triggers may be useful in more rational selection of therapy.

Persistent AF, on the other hand, requires an intervention for termination to occur.4 In the persistent form of AF, the substrate for arrhythmia and changes in the substrate due to remodeling become more important, as is depicted in Figure 4. It is specifically electric remodeling that is important from a therapeutic point of view in persistent AF because an important feature of this aspect of remodeling is that it is reversible. Successful therapy for this form of AF needs to target both triggers and substrate/electric remodeling. The observation that adding verapamil to an antiarrhythmic drug helps to prevent immediate and early recurrence of AF after electric cardioversion19 and that more extensive ablation in the posterior left atrium as well as around the pulmonary
veins has broader application for persistent AF than simple pulmonary vein isolation would fit with such a concept. The problem is that trying to determine the triggers in an individual patient and the relative importance of substrate and remodeling is not really possible in most instances.

Another concept from basic research that is captured in the schema in Figure 4 is that AF tends to progress, ie, “atrial fibrillation begets atrial fibrillation.” This concept is depicted in the schema as a progression from paroxysmal through persistent to permanent AF over time. How frequently and rapidly such a progression actually happens in an individual patient and whether or not it occurs in all patients are unknown. Furthermore, the reverse phenomenon, “sinus rhythm begets sinus rhythm,” has not been convincingly demonstrated in patients, although most of the electric and contractile atrial remodeling that occurs in animal models appears to be reversible. It should be emphasized that the bulk of the evidence for such “reverse remodeling” in the atria is from animal models, and the clinical relevance of this concept remains unclear. However, structural remodeling (fibrosis) that occurs when AF coexists with more extensive structural heart disease or when AF is allowed to persist for long periods is much less reversible, although it may be at least partly preventable with angiotensin-converting enzyme inhibition. A clinical counterpart to this prevention aspect of therapy with angiotensin-converting enzyme inhibitors has been observed in clinical situations, in which it has been shown that these drugs seem to retard development of AF in certain patient subsets. Nevertheless, once extensive structural remodeling (fibrosis) has occurred, substrate/structural remodeling becomes the dominant feature of the pathophysiology. Dominance of structural remodeling is manifest as inability to maintain sinus rhythm despite aggressive therapy. Patients who have extensive fibrosis of the atria become a major contributor to the clinical category of permanent AF (right side of box in Figure 4), those for whom attempts to maintain AF are abandoned. For patients with permanent AF, the strategy of controlling the heart rate becomes the primary mode of heartbeat control.

The schema also incorporates the concept of ubiquitous modulating factors in a fashion similar to that shown in Figure 2. There are clearly clinical situations in which modulating factors are dominant in the pathogenesis of AF. The best clinical examples of the dominance of modulating factors are the AF that is associated with hyperthyroidism and that which occurs after recent cardiac surgery. In these clinical situations, removal or waning of the modulating factor, eg, excessive thyroid hormone and inflammation, is the primary modality of therapy.

However, because of some of the aforementioned shortcomings and again because the focus is on AF itself, the schema in Figure 4 does not fully satisfy the need for a conceptual framework at the bedside. The missing pieces can be assembled in a scheme that goes beyond those in Figures 2 to 4, the trialist’s approach—outside the box in the current metaphor.

The Trialist’s Approach: Outside the Box

The trialist’s approach to the problem of AF brings a certain amount of pragmatism and a different scientific discipline to bear on the treatment of AF. Aside from the details of patient selection, end point selection, control of bias, and statistical considerations, the trialist contributes in a conceptual manner. Some aspects of this approach are outlined in Figure 5. In the trialist’s approach, the concepts encompassed in Figures 2 to 4 are reduced to a simple box. It is not important to understand the nuances within the box. The trialist starts with broad concepts such as who gets AF, the consequences of AF, and which of the latter are measurable in an unbiased fashion. These questions help to form the basis of patient enrollment criteria and end point selection. The trialist then constructs an experiment that applies a treatment and assesses its effect on the end point. A number of new elements to be considered are incorporated in such an approach.

The first issue concerns the variety of clinical situations in which AF is found. The trialist’s approach more fully takes
TABLE 1. Some Measurable End Points or Outcomes Associated With AF

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Rhythm End Points</th>
</tr>
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<tbody>
<tr>
<td>Palpitation</td>
<td>Measures of rhythm control</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Measures of rate control</td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>Others</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Many others less commonly</td>
<td></td>
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</table>

Clinical Events Other Clinical Measures

<table>
<thead>
<tr>
<th>Clinical Events</th>
<th>Other Clinical Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/thromboembolism</td>
<td>Functional capacity</td>
</tr>
<tr>
<td>Death</td>
<td>Quality of life</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Cognitive function</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Ventricular function (when reduced)</td>
</tr>
<tr>
<td>Others</td>
<td>Others</td>
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Composite End Points Others

<table>
<thead>
<tr>
<th>Composite End Points</th>
<th>Others</th>
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<tbody>
<tr>
<td>Appropriate composites of those listed above</td>
<td>Cost and cost-effectiveness</td>
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</table>

into account the epidemiological features of AF. Clearly, there are patients who seem to have AF as their only problem without any apparent “cause.” In such patients genetic factors may be important, and the pathogenesis probably most closely mimics that seen in models developed in healthy animals. Familial linkage studies to identify the genetic substrate for AF are important and promising. The majority of the patients identified in studies to date, however, are much younger than the overall population with AF. It remains to be determined whether the genetic substrate noted in younger patients with primary “electric” disease plays a role for the majority of patients in whom an interaction between age and a diseased atrial substrate appears to be dominant. Whether the genetic basis for AF in the overall population is a reflection of an interaction between genetically mediated electric disease and the environment or an entirely different set of disease processes related to age, hypertension, and vascular disease remains to be determined. Patients with primary genetic AF are a small part of the overall prevalence of AF in population studies but may be a larger part of the prevalence among those patients referred to cardiac arrhythmia specialists. This type of patient is depicted in Figure 5A. It is much more common, however, that AF is associated with some other disease process (Figure 5B through 5D). Common cardiac conditions associated with AF include hypertension, coronary heart disease, valvular heart disease, and congestive heart failure.

The next step for the trialist is to review the clinical outcomes associated with AF to define end points for clinical trials. Table 1 lists some of the outcomes or measurable end points associated with AF, and Table 2 lists the ultimate objectives of therapy for AF. The concepts in Tables 1 and 2 are embodied and interrelated in Figure 5 by listing symptoms, morbidity, and mortality as the ultimate objectives of therapy. In Table 1, several measurable end points are really means for achieving the ultimate objectives. It is apparent after this exercise, for example, that suppression of AF and control of heart rate in AF are no longer the ultimate objectives of therapy, particularly in patients who might be epitomized in Figure 5C and 5D. In fact, treatment of arrhythmia per se, although a useful end point for determination of whether a treatment is antiarrhythmic, does not guarantee a good clinical outcome or achievement of the ultimate objectives. Several recent trials of AF suppression by antiarrhythmic drugs compared with heart rate control have not demonstrated any clear evidence of clinical benefits of drug-induced AF suppression in the elderly AF patient with stroke risk factors.

The reasons that even effective treatment of AF itself may fail can be found in a stepwise review of Figure 5. In the situation outlined in Figure 5A, measurement of the effect of treatment on AF itself is a reasonable end point because AF is the only identifiable problem in such patients. However, in this situation the ultimate goal of therapy is relief of symptoms, because morbidity and mortality associated with AF in the absence of heart disease are probably very infrequent. Nevertheless, one must assess the safety of a therapy that itself may cause symptoms, morbidity, and mortality, and therefore even in this situation morbidity and mortality need to be considered. Huge numbers of patients would be required to establish safety, particularly for event rates that might be very low (<1% per year) but that are very serious (eg, death).

Figure 5B introduces the concept that a disease process may cause AF and the AF in turn causes symptoms, morbidity, and mortality. Here again, measurement of the effect of treatment on AF itself might be a reasonable surrogate for the ultimate goal of controlling of symptoms and reducing clinical events of importance. Figure 5B also introduces the concept that treatment of the disease process might also have an impact on the prevalence of AF. However, a clinical disease that only leads to AF, with AF being the cause of all subsequent problems of that disease, is probably quite rare. Primary or lone AF leading to AF-induced cardiomyopathy might be an example.

Figure 5C and 5D illustrate the much more common and complex situations commonly encountered in clinical practice, in which the underlying disease process causes or contributes to the causes of AF, which in turn causes symptoms, morbidity, and mortality. However, the disease itself, for example, hypertension, also causes symptoms, morbidity, and mortality that are totally independent of AF (Figure 5C), and in that situation even successful treatment of AF may have much less impact on ultimate objectives. In the situation depicted in Figure 5D, which might include anticoagulation as part of the treatment mix, the impact of a particular therapy has complex effects on symptoms, morbidity, and mortality that cannot be ascribed to the effects of

TABLE 2. Ultimate Clinical Objectives for Therapy of AF

<table>
<thead>
<tr>
<th>Objective</th>
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<tr>
<td>Prevention of stroke (thromboembolism)</td>
</tr>
<tr>
<td>Preservation/improvement of ventricular function</td>
</tr>
<tr>
<td>Relief of symptoms</td>
</tr>
<tr>
<td>Reduction in mortality</td>
</tr>
</tbody>
</table>

Some of these are end points listed in Table 1, but others listed in Table 1 are a means of achieving these clinical objectives. See Figure 5.
treatment on AF itself. It is for these reasons that patient selection, end point selection, and concurrent treatment are so interdependent and so critically important in the design of clinical trials.

Other aspects of the management of AF are brought into better focus by the trialist’s approach compared with the approaches outlined in Figures 2 and 4. The first is the issue of morbidity that is actually caused by AF. One of the primary clinical problems associated with AF is stroke/thromboembolism. In fact, recent evidence suggests that anticoagulation with warfarin (not an arrhythmia treatment) is the only therapy with a known effect of reducing mortality in AF. Furthermore, AF suppression has not been shown to decrease the risk of stroke/thromboembolism in high-risk patients. Recent data suggest that only 50% to 60% of the strokes in high-risk AF patients are cardioembolic when a high proportion of the patients are anticoagulated with warfarin (unpublished data, D. Sherman, 2004). It is important to remember that AF may be a marker of other conditions predisposing to stroke, for example, aortic atherosclerosis or cerebrovascular disease. In this situation, associated drugs used in the strategy help to determine outcomes, for example, antiplatelet agents, anticoagulants, β-blockers, and angiotensin-converting enzyme inhibitors. Figure 6 outlines some of these issues surrounding thrombosis for AF in the setting of hypertension. Depicted in Figure 6 is a hypothetical construct of the mechanisms whereby hypertension and vascular disease may increase the risk of stroke in patients with AF. Hypertension, left ventricular hypertrophy, and diastolic dysfunction may increase atrial dilatation, leading to both AF and left atrial thrombus. In an unspecified proportion of patients, hypertension may not be a direct risk “factor” but a risk “marker.” In this context, AF is the result of vascular disease and reduced arterial compliance, but strokes are the consequence of factors such as atherosclerotic vascular disease, endothelial dysfunction, and atheroembolism. The role of inflammation and prothrombotic coagulation factors remains to be determined.

Although AF is inextricably linked to congestive heart failure, it is not clear which is the cause and which is the effect in the individual patient. The distinction between congestive heart failure with reduced systolic function and congestive heart failure with preserved systolic function (diastolic dysfunction) may be important in this discussion, although there are little or no data that are helpful. Atrial stretch can be an important factor in the pathogenesis of AF, and systolic dysfunction without concomitant diastolic dysfunction is probably rare. However, it is diastolic dysfunction that has been specifically identified as a risk factor for development of AF. Tachycardia-induced reduction in ventricular systolic function (cardiomyopathy), including AF-induced cardiomyopathy, is frequently mentioned as a cause of congestive heart failure with systolic dysfunction. However, there are technical problems with the measurement of systolic function during uncontrolled AF and other diagnostic difficulties. The entity of AF-induced cardiomyopathy resulting in severe left ventricular systolic dysfunction in patients without prior underlying structural heart disease is uncommon but not rare. It is more frequent, although often clinically unrecognized, that AF exacerbates preexisting systolic dysfunction and compensated heart failure. Thus, in some patients AF may be a major factor in the development or exacerbation of preexisting congestive heart failure, whereas in others the severity of heart failure is a major cause of AF. Nevertheless, these 2 epidemics of heart disease are closely linked, and their interrelationship may have prognostic importance.

Finally, there is the question of mortality. In many studies AF has been associated with increased mortality, but whether AF causes increased mortality or is an innocent bystander has not been established and probably will not be established until there is a highly effective treatment with a low risk.

The Future
Clearly, no single approach to the problem is likely to provide a complete understanding of AF and its treatment. To
progress, research and development in all these areas, inside and outside the box in the metaphor of this perspective, need to continue. Furthermore, those who work in these 3 areas need to consider the lessons that are learned in areas other than the one in which they are actually working. It is not possible in the space available to outline all the future research needs, but some critical needs in the view of the authors are mentioned below.

Information needs to travel back and forth between the disciplines. For example, the basic science models need to incorporate senescence and hypertension because they are such important features of AF clinically. Both the basic scientist and the clinical scientist need to explore the electrophysiological properties and effects of treatment on histologically unique cells recently described in the area of the pulmonary veins.31 Certainly, the success of applying radiofrequency-generated heat to the region of the pulmonary veins and left atrium in treating AF in selected patients9,20 does not seem to be adequately or completely explained by the concept of pulmonary vein “isolation.”24,25

There is much to be done in the area of clinical research. It is not even clear how much AF itself causes problems other than symptoms in the vast majority of patients. Symptoms are clearly important in management of AF. Currently, the treatment guidelines suggest that “disabling symptoms” are the basis for choosing rhythm control over rate control in treatment of AF,4 but we do not have an accepted and reliable system for quantifying the symptoms of AF.

Despite the fact that there are several published guidelines for selection of high-risk patients who need anticoagulation,44 none of these has been prospectively evaluated for their ability to predict those who are truly at high risk. A better understanding of how to categorize patients with AF and select them for various therapies is badly needed. In the area of clinical trials, there is a need to properly examine the nonpharmacological therapies against end points that are clinically meaningful.

The current paradigm of antiarrhythmic drug development has failed to produce safe and highly effective drugs for treating AF, and an entirely fresh approach is needed. Regulatory agencies currently accept and approve drug therapies (and nondrug therapies) on the basis of AF suppression as the measure of efficacy, which seems to be an incomplete approach. Surely, recent evidence suggests that arrhythmia suppression is just the first step in the development of a useful treatment, and one must then demonstrate the clinical impact of AF suppression. It is also not clear that safety of a drug in high-risk groups, eg, those with extensive heart disease, such as previous myocardial infarction and congestive heart failure, translates into safety in patient groups with AF that more commonly experience different modes of death.45

An emerging story in the management of AF is the increasing importance of modulating factors. In this regard, we need to broaden our concept of what constitutes “antiarrhythmia” therapy in case of AF. In conclusion, it is fair to say that we have “miles to go before we sleep.”

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References


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