Individualized therapy in patients with atrial fibrillation: new look at atrial fibrillation

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Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with significant morbidity and mortality, the so-called AF burden. Despite significant progress in the understanding, the mechanisms and pathophysiology of AF treatments are often unsatisfactory. This in part may be related to the complexity of this arrhythmia, as well as its evolution overtime. Atrial fibrillation has many aetiologies and underlying causes. The anti-arrhythmic drugs (AADs) and interventions aimed at controlling AF should therefore be based on aetiology and associated conditions, rather than electrophysiological mechanisms. The current guideline in the management of AF in most part is based on safety and outcome. This review will discuss the approach to management, based on primary prevention of AF with the aim to target at risk factors, triggers, specific substrates related to aetiology rather than mechanisms. The development of new pharmacological agents and therapeutic strategies should consider not only evidence based, but also include patient-specific personalized context system biology and pharmacology; otherwise, we will continue to see moderate drug efficacy at best and negative results and outcomes.

Keywords
Antiarrhythmic drugs • Arrhythmias • Atrial fibrillation

Introduction

Atrial fibrillation (AF) is a rhythm disturbance of many aetiologies as shown in Figure 1 and has been known to physicians and investigators for more than a century.¹ There is no other arrhythmia than AF that has been studied so extensively. We have thus enjoyed more than a 100 years of progress in the understanding of the mechanism(s) and pathophysiology of AF and yet 100 years of insufficient success or almost failure in the effective medical management of this arrhythmia.

This review will briefly discuss the need in the paradigm shift of AF management based on mechanisms to aetiology.

First, AF is a very complex and evolving arrhythmia. Complexity and interplay exist among triggers, substrates and mechanisms of each type of AF, i.e. paroxysmal, persistent, long–lasting, and permanent form of this arrhythmia. Anti-arrhythmic drugs (AADs) remain the mainstay in the management of AF. The discoveries of AADs and surgical intervention are mostly based on hypothetical mechanisms that are developed in different models throughout the years. As most AADs are developed and initially investigated, either in theoretical models, single cells, isolated tissue samples or instrumented different animal models, they lack the consideration of complex interplay of mechanisms in specific substrates such as hypertension (HTN), diabetes mellitus (DM), coronary artery disease (CAD), congestive heart failure (CHF), hypertrophic cardiomyopathy (HCM), etc. as well as the neurohormonal, gender, age, and race. Therefore, expecting that a given pharmacological agent or surgical intervention results in the same efficacy is unrealistic. This picture has become more complex as we have learned the importance of various forms of atrial remodelling, i.e. electrical, mechanical, structural, and anatomical (contractile) remodelling. Table 1 summarizes the progress made in the last two decades.

Different societies have developed separate guidelines to focus on and consider economical, social, environmental issues relevant to specific populations.² –⁴ The goal of therapy in AF is to maintain sinus rhythm, control heart rate, avoid recurrences and remodeling, prevent AF burden in general, such as heart failure (HF), stroke, and improve quality of life and outcomes. Multiple risk factors, clinical conditions, and biomarkers have been recognized as shown in Table 2. It is important to distinguish between risk factors, risk markers, and biomarkers. Atrial fibrillation risk factors are clinically measurable indicators of biological process that relates to AF. Risk markers are proxies to an AF-causing process, but do not contribute to them to the biology of AF. Biomarkers are anything that can be used as an indicator of a particular disease state, such as electrograms, echocardiograms, and genetic analysis, etc.⁵ Risk predictors are not necessarily the same as efficacy predictors in individualized cases as it was wrongly assumed in cardiac arrhythmia supression trial (CAST) study. Our current risk factors are too non-specific. This is why we are treating too many patients unnecessarily, and on the other hand missing patients with AF and sudden cardiac death.

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If we follow the same path as in the CAST trial, we will witness another CAST study as recently reported in the PALLAS trial. The PALLAS trial examined the efficacy of dronedarone in patients with AF, where the trial design was based on the outcome, i.e. the total cardiovascular mortality and hospitalization showed favourable results. Paradoxically, when the same agent was used in high risk patients with CHF who had AF it increased rate of CHF, stroke, mortality and hospitalization noted that prompted early termination of trial. This emphasizes that AF in patients with CHF is different than patients without CHF.

The new concept of atrial-specific AADs such as IKS blockers like vernakalent is appealing, but only effective in at most 60% of recent onset AF and needs to be tested in different patient populations.

Recently, the consensus report of the European AF network proposed the pathophysiology and the aetiological-based management of AF. Currently, AF is classified by duration (paroxysmal, persistent, long-standing persistent, permanent) and by the extent of AF-causing symptoms (EHRA score I–IV, or CCS-SAF score 0–IV). The symptom classification reflects the need for therapeutic interventions, especially rhythm control therapy. In part, the duration of AF gives a simple reflection of the extent of ‘atrial structural damage’, but this is a very indirect assessment at best. A classification of AF types based on the underlying pathophysiology, in contrast, could help to better select therapies for specific AF patients based on the type of underlying cause and/or the degree of atrial damage. Thereby, the guideline-supported recommendation to treat underlying conditions would be substantiated. Therefore, to better guide therapy, the group proposes a classification of AF types based on the presumed AF-causing mechanisms, the validity of which requires further clinical studies.

The 2010 European Society of Cardiology guidelines for the management of AF in selecting appropriate AADs focused on safety and effectiveness rather than on different aetiologies and mainly on secondary prevention.

**Specific conditions**

### Hypertension and hypertensive heart disease

Hypertension is the most common risk factor and aetiology related to AF. By the time HTN is diagnosed in most cases, hypertensive heart disease has taken place and subsequently diastolic dysfunction and atrial remodelling has occurred. Therefore, investigation should focus on this aetiology to early treatment and intervention to prevent this process. Although angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are demonstrated in many trials to be effective to control HTN,
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disappointing results were observed in their use in patients with AF.
Likewise, multiple negative studies reported on the use of upstream therapies in patients with AF. Similarly, multiple randomized trials have failed to show any benefits of ACEIs and ARBs in the prevention of AF. Although theoretically it makes sense, the negative effect maybe because of the trial design and wrong patient population selection.

**Congestive heart failure**
Congestive heart failure remains to be one of the most important risk factors for AF, more complicated than HTN and AF. Atrial fibrillation with uncontrolled rate may cause CHF and CHF may also cause AF. Management in this is quite different.

**Coronary artery disease and acute coronary syndrome**
The CAD increases the risk of AF 4–5 folds. As inflammation is considered a precursor of CAD, coronary plaque formation and acute coronary syndrome, management should consider statin, beta-blockers, ACEs and ARBs; although multiple randomized controlled trial demonstrated their effectiveness in CAD, their effects on AF prevention and recurrence are less clear.

**Cardiomyopathies**
The various forms of cardiomyopathies, i.e. HCM, arrhythmogenic right ventricular dysplasia cardiomyopathy (ARVD/C), and other forms of cardiomyopathies are associated with increased risk of AF and adverse outcomes. Inflammation plays a significant role in all of the above conditions leading to atrial fibrosis as the final common pathway. Innovative therapies such as anti-fibrosis and anti-inflammatory targets to specific aetiology warrant further investigation as AF results from multiple and complex interactions.

**Future directions**
In the future, the management of AF will be aetiology-based as proposed by Bax et al. Furthermore, the new trials should be designed to look at early intervention before remodelling takes place. Obvi-
ously, this may not be feasible and justified to put young individuals on pharmacological therapy at an early age. Likewise, the marginal efficacy and safety of commercially available drugs have stimulated the development of new compounds in two major directions, such as modification of existing AADs and designing drugs with new targets. As fibrosis and inflammation form the final common pathway in many of the aetiologies of AF shown in Figure 2, anti-inflammatory and anti-fibrosis agents are appealing. The European Society guidelines have included early treatment and intervention for primary and secondary prevention of AF and proposed the early treatment of AF for stroke prevention trial (EAST trial).

**Summary**
The mechanisms contributing to the initiation and perpetuation of AF show a high diversity and inter-individual variability. The functional and structural changes in the atria can promote AF by a variety of processes that may involve ion-channel remodelling, inflammation, atrial fibrosis, apoptosis, loss of cell–cell contacts, altered autonomic tone, cellular hypertrophy, and deposition of amyloid. To develop individualized therapy for AF, a classification of the arrhythmia based on the pathophysiological changes in the atria needs to be developed. The new diagnostic tools for AF classification might include invasive and non-invasive electrophysiological measurements, biochemical markers and imaging techniques. Overall, AF is a progressive disease and a moving target and requires patient-tailored therapy for AF, as there is no one size fits all.

**Conflict of interest:** none declared.

**References**