Europace (2008) **10**, 21–27
doi:10.1093/europace/eum276

POSITION PAPER

Delayed rhythm control of atrial fibrillation may be a cause of failure to prevent recurrences: reasons for change to active antiarrhythmic treatment at the time of the first detected episode

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Received 21 October 2007; accepted after revision 21 November 2007; online publish-ahead-of-print 17 December 2007

KEYWORDS
First-detected atrial fibrillation;
Antiarrhythmic;
Angiotensin;
Atrial remodelling

Atrial fibrillation (AF) is associated with impaired functional capacity and quality of life and significant morbidity and mortality. The current management approach fails to maintain stable sinus rhythm (SR) in the majority of patients. For many years, guidelines have recommended antiarrhythmic treatment of a first AF episode only if the AF is poorly tolerated, a position that has been reinforced by studies showing no mortality or morbidity advantage of rhythm control over rate control. During the last decade, research has shown mechanisms of self-perpetuation of AF based on electrophysiological and structural remodelling induced by AF itself. There is mounting evidence that '*lone*' AF is because of a host of factors, some of which may be easily treatable, such as hypertension, sleep apnoea, and obesity, thus allowing secondary prevention at the time of the first episode of AF. According to these concepts, lack of early intervention could be one of the reasons for long-term failure of maintenance of SR. In this position paper, we propose testing the working hypothesis that if an SR maintenance strategy is selected, treatment of AF should commence at the first-detected episode and should be based on a double strategy of SR restoration and aggressive treatment of associated conditions that promote atrial remodelling.

Introduction: atrial fibrillation, a growing clinical problem

In developed countries, a progressively ageing population and better survival from chronic conditions such as hypertension and heart failure has led to a dramatic increase in the prevalence of atrial fibrillation (AF). It has been estimated that between 2.3 million and 10 and 12 million individuals in USA and European Union, respectively, have AF and it is expected that these numbers will increase 2.5- to 3-fold during the next 50 years (*Figure 1*).[1–3] AF is particularly prevalent in patients with cardiac disease, but a proportion of AF patients have 'lone AF', i.e. AF that is

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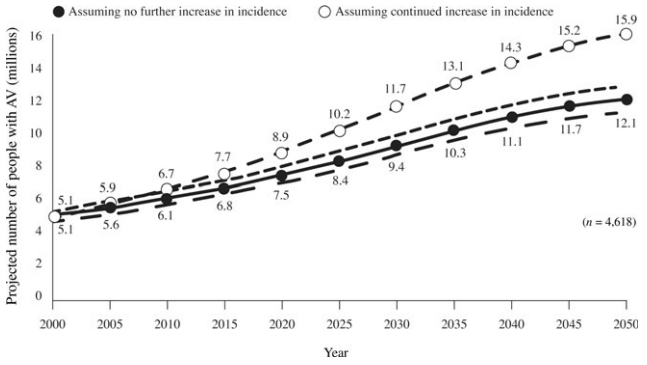

Figure 1 Projected number of persons with AF between 2000 and 2050. Reprinted with permission.[1]

not associated with structural heart disease.[4,5] AF also affects a significant proportion of younger individuals, with a prevalence of 0.7% in those aged 55–59 years.[6]

AF has a significant impact on morbidity, mortality, and quality of life (QoL),[7] which may be worse in women than in men.[7–9] This is reflected in the high rate of hospitalizations for AF.[6] Patients with congestive heart failure (CHF) are at an increased risk of AF,[10] and AF often worsens heart failure in these cases.[11–14] AF is also associated with a risk of stroke of 5% per year, two to seven times than that of people without AF.[11,15,16] Strokes are also more severe in patients with AF, and are more likely to result in permanent disability.[17]

AF often causes significant impairment in QoL that is frequently recognized by the patient only after sinus rhythm (SR) has been restored by cardioversion.[18,19] Symptoms vary with ventricular rate, underlying heart condition, and the duration of AF.[19] Importantly, a high percentage of AF episodes may be asymptomatic, which makes it very difficult to evaluate the overall impact of the arrhythmia, particularly the risk of embolism.[20,21]

AF results in considerable costs to healthcare systems, for treatment of the AF itself, and associated morbidities.[22] Most patients with AF require long-term pharmacological treatment, often including anticoagulants. Hospitalizations, which represent the major cost driver in the treatment of AF patients, are high and increasing, making AF a significant and growing economic burden[2,23,24]

Evidence that SR is better than AF

The benefits of restoration of SR include relief of symptoms, improved haemodynamic status, reduced embolic risk, elimination of the need for atrioventricular node-blocking drugs for rate control, and a reduction in the risk of mechanical dysfunction and electrophysiological remodelling.[25,26] There is evidence that the return to SR leads to a decrease in atrial size and an improvement of atrial systolic function, ventricular systolic function and functional class.[27–33] Despite all this, large carefully controlled studies have shown no survival advantage in a strategy of SR maintenance vs. one of ventricular rate control, however, these results may reflect in large part the failure in the rhythm control strategy.[34,35] Substudies have suggested that SR may be associated with improved survival,[34] and functional capacity and QoL are improved when SR is effectively maintained.[36–38]

Paroxysmal AF is often characterized by intolerable symptoms, and the need for treatment is without question in these cases. A large proportion of patients with paroxysmal AF remain in SR with paroxysmal episodes of AF for many years, indicating that substrate remodelling may not develop in all cases.[39,40] Pharmacological treatment, either for prevention of paroxysms or for early cardioversion with antiarrhythmic drugs (AAD) improves clinical status, reducing duration of the episodes and hospital admissions.[41,42]

Current treatment of AF results in high recurrence rates

Electrical cardioversion effectively restores SR.[43] However, the AF recurrence rate is high, and at one-year follow-up, only 30–60% of patients remain in SR, even if an aggressive strategy of multiple cardioversions and serial AAD use is adopted.[44] AADs can be effective in converting AF to SR, especially in recent-onset AF, but in the absence of prophylactic antiarrhythmic therapy, relapses are common (44–85% after 12 months).[45] AADs can also be effective in persistent AF, where the rate of pharmacological cardioversion can be as high as 25%.[45,46] AADs improve the chance of maintaining SR over the short- or mid-term (weeks or months). However, in patients with chronic persistent AF, long-term relapse rates can be as high as 89%, depending on the AAD and other clinical factors.[45,47] Long-term outcome of catheter ablation is, as yet, not well known, but may be unfavourable in remodelled patients. However, for patients without structural remodelling in the setting of focal AF, results may be excellent, and these patients probably should receive catheter ablation early in the course of management.[48,49] In patients with significant left atrial scarring, results of ablation are significantly worse.[50]

Evaluating the reasons for current treatment failure

Electrical remodelling (AF begets AF)

Physicians following current guidelines for the management of patients with AF will use cardioversion for a first episode only when symptoms are severe or intolerable and will consider AADs only in case of poor initial tolerance and/or recurrence, letting AF follow its spontaneous course for sometime.[5,26] However, because of time-dependent electrical and structural atrial remodelling, AF may become intractable.[51–57] We hypothesize that letting AF escape from early rhythm control, thus allowing unconstrained electrical remodelling, is one of the reasons for arrhythmia intractability later on (*Figure* 2).

Structural myocardial remodelling

Structural atrial remodelling is represented by two separate mechanisms. The first can be summarized as 'AF begets atrial dilatation', a concept supported by longitudinal studies and the effect of cardioversion to SR.[58,59] The second mechanism relates to underlying cardiovascular conditions, which may be hidden for a long time until AF emerges. Even in 'lone' AF, these conditions may be operating and should be actively sought. In fact, the term 'lone AF'

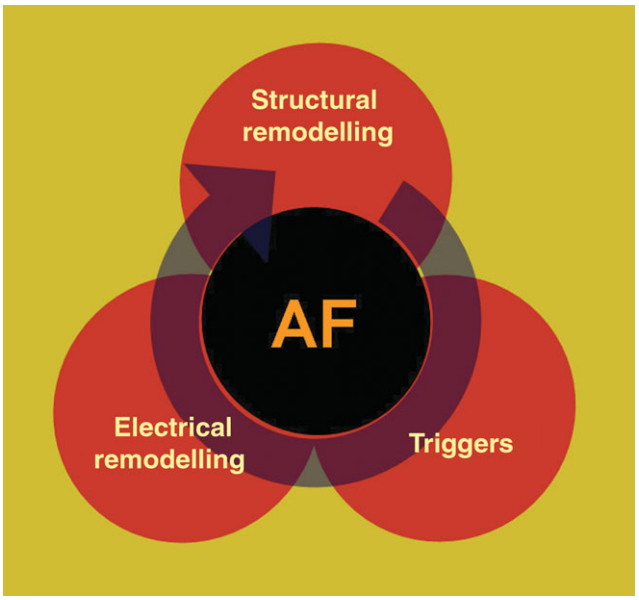

Figure 2 Schemetic representation of functional and structural factors that make the course of AF progressively irreversible.

highlights our lack of understanding of what causes AF. Epidemiological data have shown that 'lone AF' is associated with processes such as hypertension, obesity, sleep apnoea, sick sinus syndrome (especially after VVI pacing), heart failure, and even old age.[60–65] When these processes are excluded, 'lone AF' becomes rare.[66] AF may thus represent a final common pathway of chronically established heart disease (not unlike coronary artery disease) in which long-term, subtle structural and electrophysiological remodelling precedes the appearance of AF in predisposed patients.[67]

A number of observations support the association of structural myocardial remodelling with human AF. Intraoperative myocardial biopsies have shown apoptosis, increased fibrosis and structural disarray associated with AF.[68] Biochemical and histologic studies of explanted human hearts disclosed an increase in interstitial collagen content that was more abundant in association with persistent than with paroxysmal AF.[69] Electro-anatomic endocardial atrial mapping has shown large areas of decreased voltage and fragmented electrograms in subjects with SR suffering from CHF or sick sinus syndrome, processes often associated with AF.[64,70] Another interesting observation in this respect is that magnetic resonance studies have shown left atrial pulmonary vein dilation in 'lone' paroxysmal AF.[71]

Considering these observations, we hypothesize that early recognition and management of associated cardiac diseases is needed to prevent structural remodelling in a significant proportion of patients. Such a strategy may be especially advantageous in patients with a primary role of the electrical instability, but may also limit the possible role of superimposed electrical instability in patients with underlying structural disease.

Prevention of the atrial substrate

Experimental studies of electrically (pacing) or mechanically (volume overload) induced AF have shown a rapid reversibility of electrophysiological remodelling, but incomplete reversibility of structural changes, such as cell hypertrophy or interstitial collagen content.[72–75] Experimental studies have shown that treatment with enalapril[76] or candesartan[77] can, in part, prevent the structural changes induced by CHF and AF. In clinical AF, there are some encouraging data suggesting the possibility of prevention of substrate remodelling post-myocardial infarction[78,79] and in patients with hypertension, where it has been shown that angiotensin-receptor blockers may reduce the incidence of AF in comparison with beta-blockers.[67] These results raise the possibility of a specific drug-class effect, perhaps in relation to an effect on interstitial fibrosis.[76,77] Angiotensin-converting enzyme-inhibitors and angiotensin II-receptor blockers have also shown potential for decreasing AF recurrences after cardioversion when associated with AADs, suggesting possible benefits of a secondary prevention strategy.[80,81]

A study in patients with pacemakers showed electrophysiologic changes and atrial dilatation as early as 3 months after programming to VVI mode that were reversible after switching to DDD mode.[65] Another study showed an extremely high probability of maintaining SR in patients with AF and mitral stenosis subjected to balloon valvuloplasty, suggesting that even in this extreme situation, atrial electrical stability can be recovered by relieving haemodynamic overload.[82] Other potential factors underlying AF, such as inflammation, are under study, and a therapeutic potential for statins has been proposed.[83–85] The scope of substrate prevention could therefore be much wider in the future.

A new working hypothesis: early treatment of AF

Lack of a collective awareness of the importance of AF and scant scientific evidence of the underlying remodelling processes involved have contributed to delayed rhythm control as well as a lack of attention to associated cardiovascular conditions in many patients with newly detected AF. This is probably the reason why AF becomes intractable in a

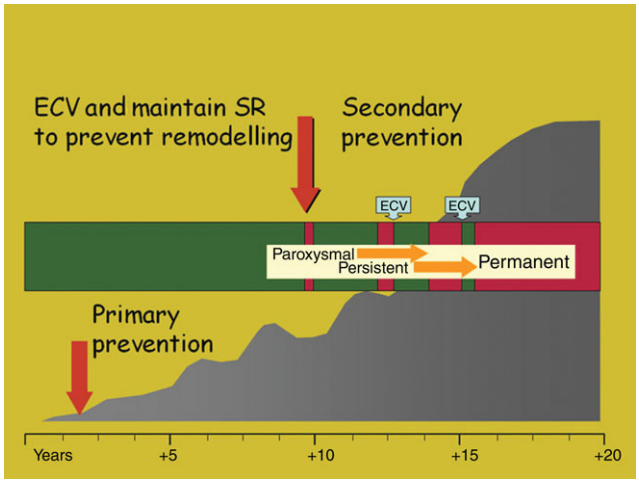

Figure 3 Hypothetical representation of the time course of atrial substrate remodeling in relation to the clinical appearance of AF and proposed interventions to slow or arrest the remodeling process.

large proportion of these patients. If AF is recognized as the result of a slow structural remodelling process, even the first documented episode of AF may be considered a late event (Figure 2). Indeed, the first documented episode may occur following a number of asymptomatic or unrecognized episodes.

Early repeated cardioversion by itself does not seem sufficient to revert remodelling enough to stabilize SR.[86] A dual strategy of early treatment of AF that includes rhythm control as well as aggressive detection and management of associated conditions may help to prevent electrical and structural remodelling and provide a window of opportunity to arrest the progression or even revert the arrhythmogenic changes in the atria (Figure 3). This comprehensive strategy has not been systematically tested.

A new AF management paradigm—clinical considerations

According to our newly proposed paradigm, rhythm control should be taken up immediately after first presentation, thus potentially slowing remodelling and 'buying time' for treatment of underlying disease processes. The first documented AF episode provides the earliest possible 'window of opportunity' to investigate and treat potential underlying causative factors such as hypertension, sleep apnoea, obesity, non-physiological pacing, excessive sports practice, thyroid problems, or excessive alcohol intake.[15,60–65] Relief of treatable haemodynamic overload because of valve disease should also be considered.[82]

AADs can be very effective early in the course of the episode, and electrical cardioversion can be used when AADs fail to obtain SR return. After cardioversion, AADs will improve the chance of maintaining SR and will prevent electrical remodelling. However, tolerability and safety are key factors in the choice of therapy. Class IC AADs are effective, safe, and well tolerated in patients without structural heart disease.[26,45,46] Amiodarone is very efficacious and may also be well tolerated if its administration is not prolonged over many months.[87] Sotalol and dofetilide bear the risk of *torsade de pointes*, which may be avoided by watching QT changes and kidney function.[26] An important consideration is the minimal necessary treatment duration with AADs. The 'reversal' of electrical remodelling in the first few weeks after cardioversion suggests that AADs may be most necessary during that time.[88] However, in some patients, more prolonged therapy may be required.

Role of catheter ablation

In addition to drugs, catheter ablation with exclusion of arrhythmogenic foci can be very effective in preventing AF recurrences, particularly in paroxysmal AF, and could be considered as an early treatment option in selected cases.[89–92] However, focal arrhythmogenic triggers can also result from atrial haemodynamic overload, as in heart failure models.[93] Therefore, the need to search for reversible underlying causes of AF remains in these cases in order to prevent late recurrences.[49,94,95]

The relatively short follow-up of most AF ablation studies, rarely exceeding 1–2 years, raises questions about the long-term prognosis, given the slow natural history of AF.[65,67] Other questions arise from the possible arrhythmogenic long-term effects of strategies consisting in widespread ablation throughout the left atrium, trying to eradicate reentry anchoring points,[90,96] because this may cause further fibrosis and create new reentry substrates.[97]

Anticoagulation

This proposition does not imply any changes in anticoagulation strategy. Patients with first detected AF should receive antithrombotic treatment according to their stroke risk profile.[26]

Conclusions

Recent concepts of the pathogenesis of AF underline the importance of slowly developing structural changes preceding a first documented AF episode and the self-perpetuating effect that AF exerts through complex electrophysiological and structural remodelling of the atria. These new ideas suggest that present recommendations for treatment of AF are too lax, and may be, in part, responsible for the difficulties in maintaining SR long-term. It appears necessary to perform new studies, including registries and epidemiological studies to reach a more complete definition of the multifactorial pathogenesis of AF. The next step should be testing a strategy of rhythm control where early cardioversion and AAD to maintain SR would be associated to multifactorial intervention on treatable pathogenetic factors. Finally, data from these studies could be used to design preventive trials based on early, aggressive intervention on factors such as hypertension, obesity or sleep apnoea, in an attempt to define cost-effective strategies and draft appropriate primary and secondary prevention guidelines.

Acknowledgements

The assistance of Michael Smith and Joan Thomas in writing this paper has been very much appreciated.

Conflict of interest: F.G.C. reports having received consultant/speaker fees from Medtronic Inc., Sanofi-Aventis, Sorin Group, St Jude Medical, and 3M Pharmaceuticals.

Funding

This work has been supported by an unrestricted grant from 3M Health Care and Meda. Funding to pay the Open Access publication charges for this article was provided by Meda Pharma.

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