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REVIEW

Risk Factor Management and Atrial Fibrillation Clinics: Saving the Best for Last?

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Atrial fibrillation (AF) is a leading cause of cardiovascular morbidity and mortality worldwide. Management of AF is a complex process involving: 1) the prevention of thromboembolic complications with anticoagulation; 2) rhythm control; and 3) the detection and treatment of underlying heart disease. However, cardiometabolic risk factors, such as obesity, hypertension, diabetes mellitus, and obstructive sleep apnoea, have been proposed as contributors to the expanding epidemic of atrial fibrillation (AF). Thus, a fourth pillar of AF care would include aggressive targeting of interdependent, modifiable cardiovascular risk factors as part of an integrated care model. Such risk factor management could retard and reverse the pathological processes underlying AF and reduce AF burden.

Keywords Atrial fibrillation • Cardiovascular risk factors • Atrial remodelling

Background

Atrial fibrillation (AF) is a leading cause of cardiovascular morbidity and mortality worldwide. This has significant and progressive impact on health care costs due to its association with increased cardiovascular morbidity, reduced quality of life, stroke and mortality [1–3]. The ageing population is an important contributor to the growing burden of AF. Cardiometabolic risk factors such as obesity, hypertension, diabetes mellitus, and obstructive sleep apnoea (OSA) have been proposed as contributors to the expanding epidemic of AF [3,4]; and, are thus potential targets for intervention to stem the expanding AF epidemic.

Atrial fibrillation is a progressive disease. Over the course of time, many patients progress from paroxysmal to persistent AF and eventually more sustained forms of AF [5,6]. Recent data suggests that both the type of AF and the progression to more persistent forms of AF are determined by the number of concomitant risk factors that are harboured [5,7]. Indeed, a recent study has demonstrated progressive injury to the atrial myocardium even after arresting AF by ablation, implicating a detrimental role of persistent risk factors [8]. For this reason, there is a need to actively identify the risk factors that may contribute to the abnormal atrial substrate in every patient with AF.

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Catheter ablation of AF has evolved as an effective therapy for drug-refractory symptomatic AF [9]. Studies have demonstrated the advantage of catheter ablation over pharmacological methods of rhythm control [10–13]. However, reports of the long-term outcomes of AF ablation demonstrate attrition in success with time [14–18]. Studies have associated cardiac risk factors with the more frequent recurrence of AF [19–21]. As such, specific mechanistic-based therapeutic options are urgently needed to modify the complex interactions between triggers and substrate maintaining AF in a given individual.

Ongoing research has unravelled many new insights regarding the pathogenesis of AF, further highlighting the complexity and heterogeneity of the disease. Atrial fibrillation management has thus become a complex process requiring focus on the rhythm and symptom management, prevention of thromboembolic complications, detection and treatment of underlying heart disease and aggressive targeting of modifiable cardiovascular risk factors [22–25]. In this review, we discuss the rationale and benefits of risk factor modification for sinus rhythm maintenance, and propose an integrated care model to incorporate risk factor modification as the fourth pillar of AF care.

Clustering of Modifiable AF Risk Factors

Cardio-metabolic risk factors frequently co-exist. Risk factors such as impaired glucose tolerance, dyslipidaemia, hypertension, and obstructive sleep apnoea (OSA) are often seen in an obese individual [26,27], which are all associated with an increased AF risk in the general population.[12,13,28] In fact, with each additional risk factor, the risk of AF and its progression increases proportionately, reaching exponential levels [26]. In the Atherosclerosis Risk in Communities (ARIC) Study, although the relative risk of AF associated with hypertension and increased waist circumference alone was 1.95 and 1.40, respectively, the presence of all components of the metabolic syndrome increased the cumulative AF risk to 4.40 [27].

Atrial Remodelling with Cardio-Metabolic Risk Factors

Atrial fibrillation is a self-perpetuating arrhythmia. The dynamic adaptive changes in the atria in response to AF, enhances the ability of the arrhythmia not only to sustain itself, but also to recur [6,28]. This remodelling process has been demonstrated to be reversible shortly after restoration of sinus rhythm [29]. By contrast, the profound structural changes seen in longer episodes of AF have been suggested to be progressive and irreversible [30,31]. It had been postulated, on the premise that it was remodelling due to AF itself that resulted in the substrate for AF, that early cardioversion would prevent adverse electrical remodelling, thus allowing ''sinus rhythm to beget sinus rhythm''. However, when evaluated clinically, prompt termination of AF did not impact the long-term maintenance of SR [32]. Thus, the role of a ''second factor'', that is, atrial substrate responsible for propagation of AF, has been suggested. Indeed, atrial changes consistent with the AF substrate have been observed in 'lone AF' patients [33]. In addition, as stated above, a recent study has observed a progressive atrial substrate even after successful catheter ablation of AF [8]. These findings argue in favour of an underlying atrial substrate responsible for AF.

Cardiac risk factors are associated with structural and electrical remodelling of the atria that forms the substrate leading to development of AF [34–36]. The maladaptive structural changes occur at the macro and microscopic level [37]. The hallmark of macroscopic change is ''atrial dilation'' [31,38]. Significant microscopic changes include cellular hypertrophy, fibrosis, apoptosis and fatty infiltration [39,40]. The complex signalling pathways underlying these structural changes remain incompletely understood and involve, at the very least, the transforming growth factor-beta 1(TGF-β1), renin-angiotensin-aldosterone system, connective tissue growth factors, and the endothelin-1 system [41–44]. The structural changes are thought to contribute to abnormal atrial conduction that favours re-entry and endo-epicardial electrical dissociation to result in AF perpetuation.

Although initial reports indicated irreversibility of atrial fibrosis [45], more recent data suggests reversibility in early stages provided enough time is allowed after reversal of inciting risk factors [46]. This has been borne out in the clinical studies demonstrating reduction in AF burden with modification of risk factors [22–24]. It is this concept of a progressive but reversible atrial substrate that forms the backbone of risk factor management. Figure 1 summarises the substrate development for AF in patients with obesity and associated cardio-metabolic risk factors, and reversibility with risk factor management.

Risk Factor Management – The Fourth Pillar in AF Management

Weight Loss as the Cornerstone of Risk Factor Management

Obesity tends to cluster with other modifiable risk factors. There is now good evidence that weight loss not only improves AF outcomes, but that it also yields beneficial effects on OSA, hypertension, insulin resistance and dyslipidaemia [22–24,47]. Critically, the benefits conferred by the initial period of weight-loss appear to be sustained in the long-term if weight-loss is maintained [24]. As such, a weight reduction strategy should form the cornerstone of risk factor management in AF.

Population studies have indicated, not only that obesity is correlated with a greater frequency of developing AF, but also that this relationship is dynamic [48]. The clinical utility