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Editorial

Non-traditional antiarrhythmic drugs as upstream and downstream dam for atrial fibrillation burden

The traditional atrial fibrillation (AF) paradigm created by Wiffels in 1995 [1] "*AF begets AF*" was recently further developed by introducing the new holistic concept of "*Atrial Cardiomyopathy*" (ACMP) [2]. Corresponding to this pathophysiological concept, AF is the result (*marker*) of any type atrial electrical and structural remodeling induced by risk factors and at the same time AF itself induces atrial remodeling acting as a risk factor for ACMP. The new concept is important to understand the "*two hits*" hypothesis for AF prevention: prevention and treatment of risk factors and prevention and lowering of AF burden (Fig. 1).

Agents that target the remodelling process could prevent new-onset AF by behaving as non-traditional AAD (upstream therapy). Activated renin-angiotensin-aldosterone system (RAAS) is up-regulated in AF [4,5] and angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) proved encouraging in preventing AF in preclinical studies [6,7] and appear, as shown by retrospective analyses and reports from the studies in which AF was a pre-specified secondary endpoint, to prevent new-onset AF in patients with LV dysfunction, LV hypertrophy and in hypertensive patients [8,9]. Statins are attractive candidates for upstream therapy particularly because the causative role of the inflammatory mechanism in AF was recently established [10,11]. However in an adequately designed RCT [12] statins failed to show a beneficial preventive effect. Evidences from RCTs have shown that mineralocorticoid receptor antagonists (MRA) reduce new-onset atrial arrhythmias in patients with heart failure with reduced ejection fraction in parallel with improvement of other cardiovascular outcome [13]. The positive impact of MRA was also shown in patients with heart failure with preserved ejection fraction [14]. Recently the RACE 3 study [15] offered new insights for upstream therapy. In this study of patients with mild and moderate heart failure upstream rhythm control including ACEI and/or ARB, MRA, statins, cardiac rehabilitation therapy, and intensive counselling on dietary restrictions, exercise maintenance, and drug adherence confirmed the importance of assessing underlying conditions in targeting upstream therapy and that targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent AF.

Conversely, classic antiarrhythmic drugs (AAD) are only moderately effective likely because they target directly the electrophysiological properties and do not modulate the complex signaling mechanisms involved in AF-promoting atrial remodeling and its perpetuation. Moreover there are important warnings concerning the safety of AAD as shown by repeated meta-analyses and systematic reviews proving the moderate to low efficacy of current AAD in controlling sinus rhythm at the expense of frequent side effects including severe proarrhythmia and a high withdrawal rate [16]. New drugs are continuously developed in parallel with the evolution of knowledge; however, a huge gap exists between currently available AAD and contemporary practical expectations [17]. Newer drugs should target both the extrinsic and intrinsic drivers and mechanisms of ACMP and AF including genetic background, atrial proteomics and metabolomics, fibrosis, inflammation and neurobiology factors [18]. Recent studies have diversified the cellular and molecular targets for AF therapy. Not only cardiomyocyte but also fibroblasts, macrophages or adipocytes could represent potential new targets. The molecular targets responsible for the AF-related electrophysiologic abnormalities and also those involved in AF progression as calcium-dependent intracellular mechanisms or inflammatory drivers are promising targets for a new framework for AF drug developement [10,11,19].

In the present issue of the Journal [20] Berlin et al. present the design of a phase II randomized study with a new non-traditional antiarrhythmic molecule, OMT-28, aimed to demonstrate the ability of sinus rhythm stabilization after electrical cardioversion of AF. OMT-28 is a synthetic analog of 17,18-epoxyeicosatetetraenoic acid, an active lipid mediator derived from the omega-3 fatty acid eicosapentaenoic acid. Omega-3 epoxyeicosanoids were demonstrated to prevent cardiomyocyte calcium overload, to protect from hypoxia or reoxygenation injury, to improve mitochondrial function and to inhibit pro-inflammatory signals through inhibition of NF-kβ [21]. The proposed study will test 3 different dosages of active drug (4 mg, 12 mg and 24 mg) versus placebo in a 1:1:1:1 design. One important attribute of the study, fulfilling the modern requirement for AF screening, is the calculation of AF burden with continuous rhythm monitoring using insertable loop monitoring devices. In this way the study is aimed to demonstrate, besides the safety, pharmacokinetics and pharmacodynamics of the new molecule, the impact of a potential new antifibrillatory drug on the real AF burden (including silent AF) and also the rate of recurrences and time to recurrences.

There are several important conclusions to be drawn from this study. First, it emphasizes the imminent need for a new paradigm [22] in the prevention and treatment of AF but also in the enlarging the concept of AADs beyond the traditional concept of the pure electrophysiological actions as described in the historical Vaughan-Williams-Singh classification of AADs [17]. Second, this study could help to gain further insights into the complexity of

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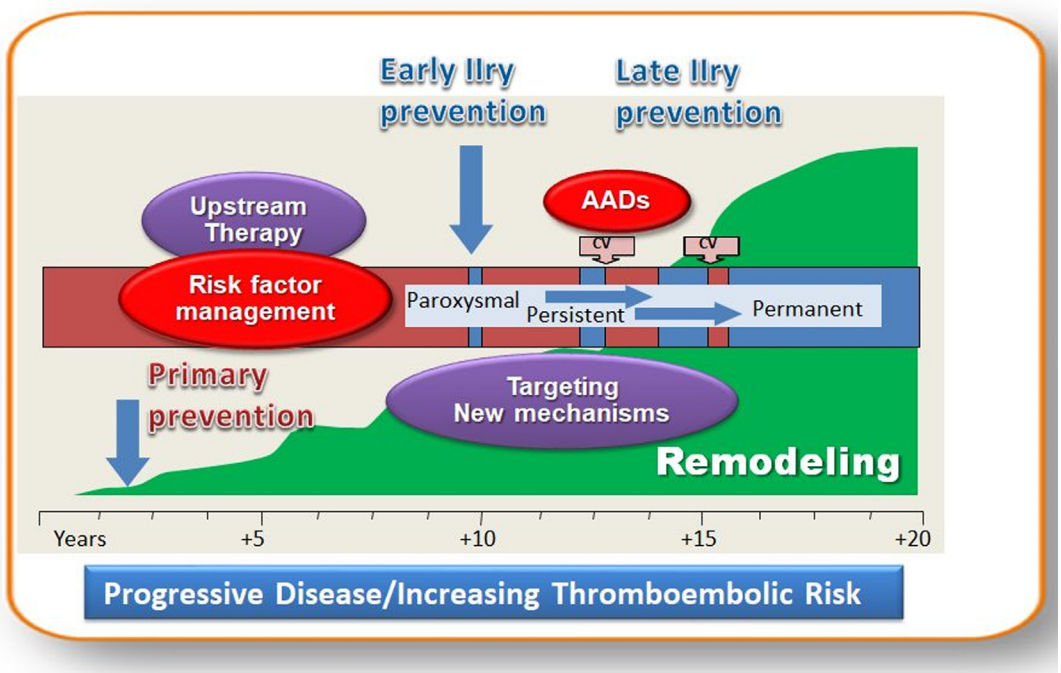

Fig. 1. Prevention of AF and AF burden. CV: cardioversion; AADs: traditional anti-arrhythmic drugs Modified after Cosio [3].

AF beyond a simple electrical phenotype. Not surprisingly there is growing evidence in favor of an intimate relationship between inflammation and AF initiation and perpetuation [10,11]. Not only inflammatory biomarkers such as interleukin-1β are correlated with prevalence and prognosis of AF. but the arrhythmia mechanism its involves multiple inflammatory pathways, which offer attractive targets for the development of new therapeutic options based on anti-inflammatory, non-traditional AAD [23].

Large and unexpected doors are now opening to new AAD development confirming the prediction of Hamlet: "*There are more things in heaven and earth, …. Than are dreamt of in your philosophy*".

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