Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with significant morbidity and mortality. It is most often a progressive disease secondary to continuous structural remodelling of the atria, which is related to changes associated with ageing, and to deterioration of underlying heart disease. Current management aims at preventing the recurrence of AF and its consequences (secondary prevention) and includes prevention of stroke, ventricular rate control, and rhythm control therapies including antiarrhythmic drugs and catheter ablation [1]. The concept of prevention of AF with interventions against the development of substrate and risk factors for AF has emerged as a result of experiments that suggested novel target for mechanism-based therapies. Upstream therapy refers to the use of non-antiarrhythmic drugs that modify the atrial substrate or target specific mechanisms of AF to prevent the occurrence or recurrence of arrhythmia. Such agents include mainly angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), statins and polyunsaturated fatty acids (PUFAs) [2].

**RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM BLOCKADE**

There are many evidences that the renin-angiotensin-aldosterone system (RAAS) is involved in the genesis of AF. There is also experimental evidence of antifibrillatory and antifibrotic actions of ACEIs and ARBs in various AF models. Their potential mechanisms of action include hemodynamic, antiproliferative, anti-inflammatory, and antioxidant effects that may prevent the development of left atrial stretch and enlargement, interstitial fibrosis, and adverse atrial electrical remodelling. This results in a shortened duration of the action potential, abnormalities of intracellular calcium handling, and alteration in cell-to-cell conduction [3-4]. RAAS activation increases the risk of development of AF by aggravating atrial remodelling in the setting of structural heart disease. Conversely, once AF has developed, RAAS activation in the fibrillating atria perpetuates AF. Angiotensin II also contributes to arrhythmogenesis by modulation of ion channels and gap junctions and this indicates that blocking the RAAS may offer an incremental benefit in patients with AF beyond the therapeutic effects on hypertension and heart failure.

Currently, it is recognized that there is a sustained reduction in new-onset AF in patients with significant underlying heart disease (such as left ventricular dysfunction and/or hypertrophy) treated with ACEIs or ARBs, but evidence is less convincing in patients with moderate structural heart disease and recurrent AF [1-2, 5-6]. Negative results were reported in two large prospective studies with ARBs in patients with no or minor structural disease and this clearly raised the issue that these treatments may not offer the same benefit in all patients [7-8]. The negative results in patients with documented paroxysmal AF without structural heart disease in the ANTIPAF study are certainly disappointing but do not demonstrate that RAAS blockade is not effective in treating AF in some other types of patients.

The ACE I/D polymorphism may favor AF under certain circumstances and might then modulate the response to ACEIs and ARBs. Liu et al. conducted a meta-analysis on the association between ACE I/D gene polymorphism and AF risk [9]. They found that the ACE I/D polymorphism recessive mutation (DD genotype vs ID and II genotypes) was associated with an increased risk of AF, with a significant and homogeneous association between ACE I/D polymorphism and hypertensive AF (OR [odds ratio] = 2.3). It thus seems that ACE I/D polymorphism may play a role for the development of AF in hypertension and apparently not in other conditions, while at the same time RAAS blockade appeared the most efficient to prevent new AF in heart failure and not in hypertension [6]. Hypertension is a condition in which incidence of AF is relatively low compared to other populations with recurrent AF or heart failure. It is possible that polymorphism plays a role only in conditions with a low or intermediate risk of AF. It may have a less important role in patients highly prone to AF, with high mechanical or electrical remodelling in heart failure and/or in secondary prevention of AF [10]. Whether RAAS blockade may prevent AF and then AF-related events more efficiently in patients with low, intermediate or high level of ACE has to be determined.
More generally, the fact that ARBs sometimes failed to prevent AF may be explained by a possible matter of target and timing. Patients with healthy heart will probably not benefit from RAAS inhibition. It is also likely to be the case for patients in whom disease is old and the remodelling or substrate definitely established, and moreover if they are treated for a rather short period. As always when one analyzes the benefit of a therapy in AF, one should probably not limit the evaluation to occurrence of AF episodes, but also to AF-related events and to hard clinical endpoints. This benefit, if clinically relevant, will possibly not appear in any rhythm analysis or AF burden quantification. Neither the VALUE nor the GISSI-AF studies have shown improved outcome with ARB-based therapy in AF patients. However, it has to be pointed out that RAAS blockade reduced cardiovascular morbidity and mortality in patients with persistent AF in the LIFE trial and in ACTIVE-I [1].

Overall, there are reasonably convincing clinical trials data indicating that RAAS blockade is effective for the primary prevention of AF in some patients, while several other studies failed to show any benefit for ARBs in preventing recurrences of paroxysmal AF or evolution to more sustained form of AF, probably because some, but not all, patients respond favorably to these agents for prevention of AF. RAAS inhibition may be effective across the long continuum of AF, from prevention of AF to reducing several of its consequences in some patients in whom sinus rhythm can no longer be restored.

STATINS

An association between inflammation and development of AF has been described, and the potent anti-inflammatory and antioxidant properties of statins may make them effective in preventing the development of AF [11]. Several meta analyses have been published on the effect of statins on incidence or recurrences of AF and they had surprisingly different conclusions [12-16]. A main reason for discrepancies in these meta-analyses is that they focused on different types of AF.

The most convincing results for the efficiency of statins against AF are for the prevention of postoperative AF. The benefit of statin therapy is significant in prevention of postoperative AF and AF reduction ranges from 40 to 60% in this setting [13-14]. Statins are associated with reduced risk of postoperative AF episodes and shorter hospital stay after cardiac surgery and an earlier therapy results in more profound benefits [13]. Some mechanisms could account for the relatively clear effect of statins in such setting. Myocardial damage is commonly encountered after coronary procedures. It is a potential risk factor for AF and statin treatment might in part abrogate myocardial tissue injury. In addition to the findings in patients undergoing cardiac surgery, it was recently found in a retrospective cohort study following major noncardiac surgery that statin use was associated with a lower rate of postoperative AF. After adjustment for risk factors and surgery type, risk for postoperative AF remained significantly lower (20% risk reduction) among statin-treated patients [17].

In primary prevention of non postoperative AF, the GISSI HF investigators found a beneficial effect of rosuvastatin in reducing AF occurrence in patients with HF. More precisely, the difference was not significant at unadjusted analysis for new onset AF, but it became significant after adjustment for several variables [18]. Such an adjustment is usually not needed in a randomized controlled trial, and several other issues have been raised on the primary prevention of AF with statins [19]. In the pooled analysis of the long-term trials by Rahimi et al., none of the included studies were performed in patients with a specific history of AF. It may consequently be considered as an analysis on the effect of statins for primary prevention of AF. Statin therapy was not associated with any relevant benefit for the prevention of AF [16]. A too short follow-up duration in these patients might have disadvantaged the active therapy with statins. However, the evaluation of the treatment effect (with an OR very close to 1.00) in more than 100,000 patients really suggests there is not a major benefit for the primary prevention of AF with statins.

In secondary prevention of AF, statins were not associated with an increased probability of maintaining sinus rhythm following electrical cardioversion of persistent AF in the pooled analysis by Bhardwaj et al. [15]. However, two randomized trials have been more recently published. Xia et al. found that rosuvastatin decreased the early recurrence of AF following successful electrical cardioversion (relative risk reduction of 65%) [20], and it was found in the STOP AF trial that high-dose atorvastatin was associated with a similar, although not significant, reduced risk of recurrence of AF after cardioversion of 62% when one considered patients free of events at the end of follow-up [21]. If one focuses on the randomized trials published today providing information on the effect of statins for secondary prevention of AF in more than 1300 patients, the mean risk reduction of AF episodes is around 40%. The significant heterogeneity in odds ratio calculations probably reflects the heterogeneity of the different clinical settings, AF mechanisms and magnitude of the benefit of statin therapy in the different groups of patients studied in secondary prevention of AF.

Since the anti-inflammatory effect of statins, one of the mechanisms for their potential antiarrhythmic capacity has been surmised to be more pronounced in high-dose statin therapy. However, it has not been possible to establish the correlation between the degree of LDL reduction and the incidence or recurrence of AF at the individual level in the studies that compared the use of statins vs. no statins, as it has been done with other cardiovascular events involving statin therapy. Based on the pooled analysis of the studies that compared more vs. less intensive statin regimens, no benefit was attributable to higher doses of statins or correlated with lower LDL levels [22].
Thus, it seems that patients’ success in lowering LDL to a given goal (< 100 or < 70 mg/dl) with statins or an increase in their statin dose has no impact in terms of AF events.

Overall, the use of statins is significantly associated with a decreased risk of incidence or recurrence of AF in some patients. However, this beneficial effect is not seen for all types of AF in all patients. The use of statins seems associated with: 1/ a lack of benefit in primary prevention of AF; 2/ a significant but heterogeneous decreased risk of recurrence of AF in secondary prevention, and 3/ a very significant and homogeneous reduction for the risk of postoperative AF. As for RAAS blockade, the magnitude of the antiarrhythmic effect of statins against AF is certainly lower than what was initially suggested. Moreover, it is finally doubtful that the term of upstream therapy is really appropriate for the role of statins in prevention of AF, since their protective effect does not appear to be significant in long term primary prevention trials, while it seems more important in acute settings like surgery to prevent postoperative AF and in some patients in secondary prevention of AF.

POLYUNSATURATED FATTY ACIDS

Intake of PUFAs from fish might have some anti-inflammatory and antifibrotic properties resulting in a beneficial effect against atrial remodelling. However, the level of evidence for their efficiency in terms of prevention of AF is currently relatively low. There have been observational studies with all their limitations. One may wonder whether patients treated with PUFAs had different characteristics and management, and possibly a different prognosis because they were better treated than other patients. In the prospective, population-based cohort of the Cardiovascular Health Study including 4815 adults older than 65, consumption of tuna or other broiled or baked fish, but not fried fish or fish sandwiches, was associated with lower incidence of AF with 28% lower risk with intake one to four times per week [23]. However, similar analyses from other large population-based studies reported no benefit on incident AF from higher fish intake [24-25]. Few randomized trials were performed in the very particular setting of prevention of AF after cardiac surgery and they had conflicting but mainly negative results [26-28]. Thus, although the theoretical background and experimental evidence suggest the antiarrhythmic effect of PUFAs, proof of efficacy in large-scale trials has so far been absent in AF.

CONCLUSION

In the primary prevention of AF, a sustained reduction in new-onset AF has been shown with ACEIs and ARBs in patients with significant underlying heart disease (e.g. left ventricular dysfunction and hypertrophy) and in the incidence of AF after cardiac surgery in patients treated with statins. In the secondary prevention setting, the results with upstream therapies are less encouraging, particularly with ACEIs and ARBs. Although the results of hypothesis-generating small clinical studies or retrospective analyses in selected patient categories have been positive, larger prospective RCTs with RAAS blockade have yielded controversial, mostly negative, results. Overall prevalence AF is likely to increase substantially in the coming decades. The haemodynamic compromise and risk of stroke in AF are associated with a significant increase in mortality, morbidity, impairment of the quality of life and this represents a substantial burden on health services. The controversy exists on whether upstream therapy may impact mortality and major cardiovascular events in patients with AF (when this therapy is not indicated for another cardiac condition), but there is little reliable evidence on how to prevent AF with other methods.

POTENTIAL CONFLICTS OF INTEREST: None to declare.

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