Rhythm control for atrial fibrillation: Non-channel antiarrhythmic drugs are en vogue

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Atrial fibrillation (AF) is the most common cardiac arrhythmia. Independent risk factors for AF are chronic heart failure and hypertension [1]. The incidence and prevalence of AF increase with the severity of chronic heart failure. Although recent trials showed that rate control can be adopted as first choice therapy [2], rhythm control still is the primary goal. Whether this also holds for patients with chronic heart failure is at present unsettled, but obviously, these patients would benefit most from sinus rhythm since with restoration and maintenance of sinus rhythm, left ventricular function, exercise capacity and maximal oxygen consumption may improve. At present, the cornerstone for rhythm-control therapy is serial ion-channel antiarrhythmic drug treatment with or without cardioversion. This strategy, however, often fails, especially in patients with heart failure. One reason is that antiarrhythmic drug treatment for prevention of AF always starts after the first development of AF, whereas the substrate for AF already has (in part) been developed during sinus rhythm, before the first episode of AF ever. Another reason is, notably, that the currently available ion-channel antiarrhythmic drugs only influence action potential duration and conduction velocity, but do not affect the substrate for AF.

New types of non-channel antiarrhythmic drugs may influence the development of the substrate. These drugs include angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, hydroxymethylglutaryl CoA reductase inhibitors (statins), aldosterone antagonists and N-3 polyunsaturated fatty acids. Mechanisms by which this ‘upstream therapy’ or non-channel antiarrhythmic drugs may prevent or reduce AF are (1) prevention of structural remodeling, i.e. the substrate for AF, e.g. by reduction of fibrosis, inflammation and oxidative stress, but also by (2) improvement of hemodynamics, including lowering of blood pressure and reducing left ventricular and atrial wall stress, and (3) prevention of (progression of) coronary artery disease.

ACE inhibitors and angiotensin receptor blockers indeed prevented new-onset AF in patients with heart failure [3,4], and the addition of an ACE inhibitor or angiotensin receptor blocker to amiodarone improved maintenance of sinus rhythm after electrical cardioversion [5]. The mechanisms by which ACE inhibitors and angiotensin receptor blockers may reduce the development of AF are diverse, as mentioned above. Experimentally, ACE inhibitors and angiotensin receptor blocker prevented left atrial dilation, atrial fibrosis and conduction velocity disturbances and resulted in a lower rate of AF induction by atrial pacing [6]. Enalapril reduced atrial remodeling to a greater extent than the combination of hydralazine and isorbidone mononitrate, suggesting that the effects of ACE inhibitors on the prevention of AF are directly related to the renin–angiotensin–aldosterone system inhibition rather than improving hemodynamics [7].

Statins are the most powerful lipid-lowering drugs at present and have additional pleiotropic effects including

See article by Shiroshita-Takeshita et al. (pages 75–84) in this issue.
attenuation of inflammation and antioxidant effects [8,9]. Since there is evidence that enhanced oxidative stress and inflammation are associated with (future development of) AF, statins may play a role in both the primary and secondary prevention of AF. Earlier, Nattel and coworkers demonstrated the beneficial effects of statin therapy with simvastatin in their atrial tachypacing model with atrioventricular block to control ventricular rate and thus prevent chronic heart failure. In concert with a reduced atrial effective refractory period prolongation and L-type Ca\textsuperscript{2+}-channel α-subunit expression, simvastatin attenuated AF promotion [10]. The dosage of simvastatin instituted in these 20- to 37-kg dogs was 80 mg/day, a higher dose than usually is administered to patients.

In the present issue of Cardiovascular Research, Shiroshita-Takeshita et al. investigated whether simvastatin also has beneficial effects on the prevention of AF in dogs with chronic heart failure [11]. In order to induce chronic heart failure, dogs (20–35 kg) were subjected to 2 weeks of ventricular tachypacing. This was done in the presence or absence of lower (20 mg, comparable to human dosages) and higher dosages (80 mg/day) of simvastatin or fenofibrate (800 mg/day), a peroxisome proliferator-activated receptor-α agonist. The latter also has been demonstrated to attenuate myocardial inflammation and fibrosis experimentally [12]. As expected by data from their previous work, no changes in atrial effective refractory periods in any of the ventricular tachypacing groups were observed. Mean conduction times, however, were significantly increased by ventricular tachypacing and prevented by both doses of simvastatin but not by fenofibrate. Long-lasting AF induction (> 30 min requiring cardioversion) was abolished by high dose simvastatin, and significantly reduced in low-dose simvastatin-treated dogs. Both doses of simvastatin but not fenofibrate prevented long-lasting ventricular tachypacing-induced AF. Interestingly, simvastatin attenuated ventricular tachypacing-induced increases of left ventricular end diastolic, and left and right atrial pressures, especially in dogs treated with the higher dose of simvastatin. Fenofibrate had no effect. Finally, ventricular tachypacing-induced atrial fibrosis was reduced in both groups of simvastatin-treated dogs but not in fenofibrate dogs. Thus, simvastatin reduced atrial structural remodeling and prevented AF induction, also in clinically relevant dosages. Less impairment of left ventricular dysfunction, as especially observed in the high-dose group, may add to the beneficial effects of statin therapy.

The present study may have clinical significance and should stimulate further work on non-channel antiarrhythmic drugs for AF prevention. Currently available ion-channel antiarrhythmic drugs are often either ineffective or have significant adverse events, or are even contraindicated. These new non-channel antiarrhythmic drugs are promising because they affect directly the underlying substrate and, importantly, have a low risk of adverse events.

The induction of the atrial substrate is affected by several pathways [13,14]. Non-channel drugs may affect several of these pathways and may probably act synergistically. In sharp contrast to clinical practice, however, in experimental studies institution of these drugs always starts before any episode of AF and even before the induction of the underlying disease. This may imply that the efficacy in clinical practice will be lower than suggested by experimental data. At present, heart failure patients start therapy with ACE inhibitors and/or angiotensin receptor blockers often before the first occurrence of significant left ventricular dysfunction. Indeed, the risk of AF is lowered in heart failure patients, both in those with a reduced and those with a preserved left ventricular function, and also in patients with hypertension, but this risk is certainly not abolished [3,4]. For drugs influencing the renin–angiotensin system, clinical evidence is available for their beneficial effect on reduction of AF, and larger studies are underway. Awaiting these trials, there is, in my opinion, enough proof to institute these drugs as soon as possible in patients with either chronic heart failure or hypertension, even before a first episode of AF. The clinical evidence for statins, however, is less clear. So far, only small scale and predominantly non-randomized studies have been performed investigating the efficacy of statins for prevention of AF, both in heart failure and non-heart failure patients and for primary and secondary prevention [15]. The results of future clinical studies have to be awaited for proof. Nevertheless, the data of the group of Nattel et al. are promising and clearly suggest clinical relevance.

New research should focus on alternative pathways that affect atrial remodeling, e.g. drugs that increase expression of heat shock proteins [14]. In this respect, it is important to remark that the doses of drugs used in experimental studies must be comparable to clinically tolerated dosages. Fortunately, in the present study the lower dose was based on human doses and was therefore clinically relevant, enabling comparison with clinical practice. Indeed, the beneficial effects of the lower dose were less as compared to the maximal but clinically not relevant dosage of simvastatin.

The authors are to be congratulated for their work and will hopefully continue, together with others, their experimental investigations in a search for ways of abolishing AF. Non-channel antiarrhythmic drugs are promising and may become first-line therapy for AF in the very near future.

References


