New therapeutic approaches in atrial fibrillation

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Abstract

In patients with atrial fibrillation, a decision must be made whether to accept the arrhythmia (rate-control strategy) or to pursue restoration and subsequent maintenance of sinus rhythm (rhythm-control strategy). Previous randomized trials have shown no difference between these strategies with respect to morbidity, mortality, or quality of life. However, new non pharmacological rhythm-control treatment strategies have emerged and have improved the likelihood of long-term maintenance of sinus rhythm tremendously.

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Introduction

From two large randomized trials [1,2] it has been learned that, in patients with atrial fibrillation who are not severely symptomatic, a rate-control strategy is not inferior to a rhythm-control strategy. A subanalysis in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management trial, however, demonstrated that a successful rhythm-control strategy was associated with improved survival [3]. Furthermore, the optimal heart rate during atrial fibrillation remains unknown and is currently being investigated in a large multicenter trial [4]. These facts, and the improving success rate of new treatment strategies to cure atrial fibrillation, further the discussion of rate versus rhythm control. New insights will be briefly discussed here, including the issue of prevention of thromboembolic complications.

New antiarrhythmic drugs

The classic Vaughan-Williams classes I, II, and III drugs used for prevention of atrial fibrillation are frequently ineffective. For instance, in the Rate Control Efficacy in Permanent Atrial Fibrillation trial, maintenance of sinus rhythm at study completion in the rhythm-control group was only 39% [2]. In addition, these drugs have serious potential cardiac and non cardiac side effects. Other more effective and safer drugs have therefore been investigated in preclinical and clinical trials. First, class III drugs have emerged that have a mechanism of action similar to that of amiodarone, but do not have the side effects. These drugs include azimilide, dronedarone, tedisamil, and SSR149744C [5–8]. Secondly, atrial-selective ion channel blockers, including AZD7009, AVE0118, and RSD1235, are a promising new group of antiarrhythmic drugs [9–11]. Finally, drugs preventing structural remodeling, inflammation, and fibrosis (''upstream antiarrhythmic drugs''), including ACE inhibitors, angiotensin receptor blockers, statins, and aldosterone blockers, may target the underlying substrate and therefore prevent atrial fibrillation [12–15].

Anticoagulation

Atrial fibrillation is associated with a 5-fold increased risk of stroke. As the risk of ischemic stroke in patients

with atrial fibrillation is related to lack of or inadequate anticoagulation, regardless of rhythm management strategy [1], restoration of sinus rhythm does not obviate the use of anticoagulant drugs in patients with increased risk of ischemic stroke. Coumarins increase the risk of hemorrhagic stroke and require frequent adjustments to the dosage. Therefore alternatives are sought.

The direct thrombin antagonist, ximelagatran, has been shown to be equally effective in prevention of stroke when compared with coumarins [16,17]. The main advantage of ximelagatran over coumarins is the predictable dose–response relationship; however, because of hepatotoxicity, production of ximelagatran has been discontinued. New, similar drugs such as dabigatran are currently under investigation.

The AMADEUS (The Atrial fibrillation trial of Monitored, Adjusted Dose Vitamin K antagonist, comparing Efficacy and safety with Unadjusted SanOrg 34006/idraparinux) trial comparing the heparin analog, idraparinux, with warfarin in patients with atrial fibrillation was terminated prematurely because more bleeding complications were observed in the group treated with idraparinux.

The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events, comparing the combination treatment of clopidogrel and aspirin with warfarin in patients with atrial fibrillation and at least one risk factor for stroke, was also stopped because the efficacy was clearly in favor of anticoagulation [18]. Furthermore, there was also no reduction in bleeding in the group treated with clopidogrel plus aspirin. Thus, up to now, alternatives for coumarins are not available, and data on new drugs are eagerly awaited.

Radiofrequency ablation and surgery

In recent years, invasive techniques have been developed in treating atrial fibrillation. Originally, linear ablations were performed, mimicking the surgical MAZE procedure. However, since the observation was made that the pulmonary veins have an important role in the initiation and maintenance of atrial fibrillation [19], there has been a rapid development of techniques targeting the pulmonary veins, using either a transvenous endocardial approach or a surgical epicardial approach. The most widely used methods are segmental ablation, targeting myocardial tissue in the myocardial sleeves around the pulmonary veins [19], and circumferential pulmonary vein isolation, completely encircling the pulmonary veins [20].

Wazni et al [21] compared pulmonary vein isolation and the use of antiarrhythmic drugs as treatment of first choice in patients with atrial fibrillation. After 1 year of follow-up, 63% of the patients receiving antiarrhythmic drugs had experienced one or more recurrences of atrial fibrillation, compared with only 13% of patients who had undergone venous ablation. Pulmonary vein isolation is especially effective in patients with paroxysmal atrial fibrillation [22]. New data also show promising results in patients with heart failure [23] and chronic atrial fibrillation [24].

However, in the abovementioned studies, follow-up was short and the patients were relatively young (mean age approximately 55 years). Only a small proportion had clinically significant structural heart disease, including the patients with heart failure [24]. Therefore, these individuals differed essentially from the typical 70-year-old patient with atrial fibrillation and hypertension or coronary heart disease. Furthermore, radiofrequency ablation in the left atrium is associated with important risks, including stroke, pulmonary vein stenosis, tamponade, and formation of an atrio–esophageal fistula [25]. Therefore, in the search for better success rates and fewer complications, techniques implementing new energy sources [26] and new approaches are being developed and investigated, including epicardial ablation procedures by (minimally invasive) surgery [27–29]. The first results are very promising and will further current discussion as to the most favorable treatment for patients with atrial fibrillation. ■

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