Towards a paradigm shift in atrial fibrillation

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Management of patients with atrial fibrillation (AF) requires knowledge of its pattern of presentation (paroxysmal, persistent, or permanent) and of its underlying conditions. These findings will guide the treatment strategy, which traditionally involves either restoration of sinus rhythm or control of the ventricular rate. Regardless of whether rhythm or rate control is pursued, adequate attention must be paid to the prevention of thromboembolic complications. The current ACC/AHA/ESC guidelines for AF management, dating back to 2006, include two striking differences compared with earlier recommendations: a stronger focus on non-pharmacological therapies, and the shifting position of rhythm versus rate control.¹

Over the last decade a range of different techniques for pulmonary vein isolation (PVI) have been developed, with or without additional line or point lesions. PVI has found its way into clinical practice, and is currently the most performed ablation in the Netherlands. Yet, despite these changes non-pharmacological therapy has remained at the bottom of the treatment algorithm for all types of AF. Both in paroxysmal and in persistent or permanent AF, non-pharmacological intervention only remains indicated after failure of at least one antiarrhythmic drug. Earlier intervention may seem attractive, as success rates for first-line PVI therapy of 60% to as high as 90% have been reported, but randomised controlled trials are scarce and criteria for patient selection have not yet been clearly defined.²

Recently, an international expert panel concluded that catheter or surgical ablation of AF should not be considered a first-line therapy in most pa-

tients. Non-pharmacological therapy should be restricted to patients with symptomatic AF, with no or only little left atrial dilation, in whom at least one class I or class III antiarrhythmic drug has failed. Other factors such as the patient's age, risk of complications of the ablation procedure and extent of associated cardiovascular disease should be taken into account as well, although there is no consensus on cut-off values.³

According to the guidelines, pharmacological therapy to maintain sinus rhythm is indicated in patients with symptoms of paroxysmal or recurrent AF, who are tolerant to the medication and can be expected to maintain sinus rhythm over longer periods of time. Typically these are younger patients without significant structural cardiovascular disease, in whom the left atrium is still relatively undamaged. Antiarrhythmic drug therapy should be discontinued if treatment remains unsuccessful. Unfortunately, current antiarrhythmic drugs are far from ideal: they have been associated with proarrhythmic effects, moderate efficacy, low tolerability and a substantial risk of organ toxicity. In September 2009 the European Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued a positive recommendation on dronedarone, a novel antiarrhythmic drug with multiple ion channel blocking effects. This new agent is indicated for prevention of AF recurrence or reduction of ventricular response in AF, in clinically stable patients with (a history of) non-permanent AF. Dronedarone promotes rate as well as rhythm control, but with the additional benefit of a significant reduction of cardiovascular hospitalisation.⁴ This is an important advantage over earlier antiarrhythmic drugs, particularly in view of the changing perception of AF. Increasingly, AF is being perceived as a cardiovascular disease, with all inherent risks, rather than a 'simple' rhythm disturbance. The RACE study, for example, demonstrated that AF patients not only had a higher risk of heart failure and pacemaker implantation, but also an increased risk of cardiovascular mortality.⁵ This is due to the fact that the

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large majority of AF patients have an underlying vascular condition, such as hypertension, diabetes, coronary artery disease, heart failure or even COPD, which often goes unrecognised until the moment AF surfaces.

Along with this changing outlook the treatment goals are expected to shift as well. Although traditional endpoints – including rhythm and rate control – will remain important in highly symptomatic AF patients, future trials will also have to address hard cardiovascular endpoints, which of course are of particular relevance to high-risk patients. This asks for a paradigm shift in the treatment of atrial fibrillation. New parameters should include cardiovascular (CV) morbidity and mortality, but importantly also hospitalisation. The possibility to prevent or delay hospitalisation is a strong indicator of quality of care. Moreover, hospital admission and subsequent interventions are substantial drivers of disease-related costs. Dronedaronone has now shown efficacy on a number of such CV endpoints. The most recent study was ATHENA, a large multicentre randomised controlled trial in over 4600 patients with paroxysmal or persistent AF and at least one additional risk CV risk factor. The primary study endpoint was time to hospitalisation for a CV event or death; secondary endpoints included death from any cause, cardiovascular death, and hospitalisation due to a CV event. Mean follow-up was 21 months. The study results, published recently in the *New England Journal of Medicine*, demonstrate a significant 24% reduction of the primary endpoint compared with placebo. In addition, a 26% reduction of hospitalisation due to AF, and a 29% reduction of CV mortality versus placebo ($p=0.03$) were observed.⁴

But there is more to dronedaronone than efficacy alone. As long as pharmacotherapy remains the cornerstone of AF therapy, we will require drugs that are efficacious in restoring sinus rhythm and/or controlling the ventricular rate. This should not come, however, at the price of a high risk of toxicity. There is an urgent need for therapies with an improved balance between antiarrhythmic efficacy

on one hand, and tolerability and safety on the other. The ultimate ideal would be an agent that at the same time reduces cardiovascular morbidity and mortality. In this respect, the promising results with dronedaronone may offer a new perspective in the treatment of AF. The ATHENA results are truly relevant, as the study population reflects the type of patients that are frequently seen in clinical practice. Randomised controlled studies among more than 6700 patients have confirmed that dronedaronone is well tolerated and safe. The most frequently reported adverse events are related to the gastrointestinal tract, followed by skin abnormalities and serum creatinine elevation, yet without any indication for renal toxicity. The risk for serious thyroid or pulmonary complications is extremely low, and there is only minimal risk of proarrhythmia. Dronedaronone therefore might deserve a prominent place in the AF treatment algorithm. ■

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N.B. See also article by De Groot et al. *NHJ* 2010;18:371-4.