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EDITORIAL

Alternatives to amiodarone: search for the Holy Grail

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This editorial refers to 'A preliminary assessment of the effects of ATI-2042 in subjects with paroxysmal atrial fibrillation using implanted pacemaker methodology' by A. Arya *et al.*, on page 458

Atrial fibrillation (AF) is the most common heart rhythm disturbance, effecting more than six million individuals in North America, Europe, and Japan. Atrial fibrillation is associated with increased morbidities, including thrombo-embolism, stroke, and decreased cardiac function. However, some patients experience debilitating symptoms and decreased quality of life for which elimination of the arrhythmia is an important goal. Although AF ablation is quickly expanding to treat some of these patients, first-line therapy remains antiarrhythmic drugs (AADs). Furthermore, there are many patients with symptomatic AF who are not candidates for ablation due to associated comorbidity. Thus, there remains a great interest in pursuing novel AAD therapy.

In spite of numerous available AADs and introduction of new alternatives, the most effective available antiarrhythmic remains amiodarone.[1–3] No oral AAD to date has proven efficacy superior to amiodarone for long-term maintenance of sinus rhythm.[4] This is in part due to the fact that amiodarone has several mechanisms of action on cardiac conduction. In addition to traditional class III effects, amiodarone also has beta-blocker, calcium channel blocker, and sodium channel blockade effects. The iodine moiety may also have independent antiarrhythmic effects. In the Canadian Trial of Atrial Fibrillation (CTAF),[1] amiodarone was shown to be superior to both class Ic (propafenone) and other class III (sotalol) AADs. After 1 year, the calculated probability of remaining in sinus rhythm was 69% for patients on amiodarone compared with only 39% in the sotalol/propafenone group. In another study by Singh *et al.*,[2] amiodarone was again shown to be superior to sotalol, with a median time to recurrence of 487 days compared with 74 days in the sotalol group. Furthermore, amiodarone is effective in reducing AF burden without causing proarrhythmia, particularly in patients with congestive heart failure or structural heart disease.[5] Amiodarone has been shown to be effective in preventing AF in heart failure patients.[5] Only dofetilide has been shown to have a comparable efficacy profile in heart failure, but with a 3.3% risk of torsades de pointes.[6]

Unfortunately, amiodarone is also one of the most dangerous AADs with a high incidence of side effects. In CTAF,[1] 18% of patients were forced to stop amiodarone because of adverse reactions, and over 5 years, it is estimated that >30% of patients will be forced to stop the drug.[7] Common side effects include thyroid disorders, photosensitivity, skin discoloration, and corneal microdeposits. More concerning are other, less common side effects which can cause severe morbidity and even mortality. These include neuropathies, pulmonary fibrosis, and liver dysfunction. Although the incidence of these side effects may be dose-dependent, amiodarone's extremely long half-life and large volume of distribution makes the incidence of side effects increase over time. Most concerning is that amiodarone may actually increase mortality, offsetting any benefit of maintaining sinus rhythm. In a substudy of the AFFIRM trial, for example, patients in sinus rhythm experienced improved mortality.[8] However, this benefit was in part offset by being on amiodarone, which was associated with an increased non-cardiac mortality (hazard ratio 1.49, $P = 0.0005$).[8] Increased non-cardiac mortality on amiodarone was also seen in the EMIAT and AVID trials, particularly cancer and pulmonary problems.[9,10]

Thus, while amiodarone continues to be used widely for the treatment of AF, alternatives with equal efficacy but lower toxicity are being sought, but with limitations. In patients with congestive heart failure, dofetilide has been shown to have a comparable efficacy to amiodarone.[6] However, the relatively high risk of proarrhythmia necessitates inpatient drug loading and the drug is not even approved in many countries. Furthermore, in patients with even mild degrees of renal impairment, the use of dofetilide can be risky. The amiodarone analogue dronaderone is being actively studied as a replacement for amiodarone and has generated the most excitement recently. Like amiodarone, dronaderone has multiple antiarrhythmic actions, including classes I, II, III, and IV without

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substantial impact on the QT interval. The drug is also non-iodinated and thus causes little anti-thyroid effect. Early studies suggested the drug may provide the benefits of amiodarone without the toxicity profile.[11] Indeed, the recent ATHENA trial has shown that dronaderone decreases both all-cause mortality and cardiovascular hospitalization in elderly AF patients with structural heart disease.[12] However, while animal data suggested that dronaderone may be a more potent antiarrhythmic than amiodarone, clinical results have shown efficacy at maintaining sinus rhythm to be less than amiodarone.[13] Furthermore, the ANDROMEDA trial demonstrated an increased mortality attributable to dronaderone in patients with severe congestive heart failure and left ventricular dysfunction.[14] Thus, while dronaderone may be a promising alternative to amiodarone, there is clearly a need to find other alternatives.

Arya and colleagues describe the efficacy of a novel amiodarone analogue antiarrhythmic agent called ATI-2042 (ARYx Therapeutics, Fremont, CA, USA) in a small-phase 2-type study.[15] Although the structure of ATI-2042 is similar to that of amiodarone, an ester modification allows for more rapid metabolism by plasma and tissue esterases. Thus, ATI-2042 reportedly has a similar electrophysiological effect to amiodarone, across several Vaughn Williams classes, while possessing a much shorter half-life of only 7 h. This shorter half-life should make this drug less prone to amiodarone's toxicities while maintaining its efficacy. Furthermore, in contrast to dronaderone, ATI-2042 is iodinated and maintains some anti-thyroid activity.

In this study, Arya *et al.* tested the efficacy of ATI-2042 on six female patients with significant burdens of paroxysmal AF and dual-chamber pacemakers. The patients were older, but had little to no structural heart disease and relatively normal-sized atria. The patients were studied in six 2-week periods (p1–p6). The initial and final periods were off drug. During the second period (p2), patients were initiated on 200 mg b.i.d. of ATI-2042 and the dose was increased by 200 mg b.i.d. during each study period to a maximum dose of 800 mg b.i.d. (p5). Atrial fibrillation burden was then calculated based on weekly pacemaker downloads to determine both the number and duration of AF episodes. ATI-2042 significantly decreased AF burden compared with baseline at all doses, with the most substantial reduction seen at the highest (800 mg b.i.d.) dose. While there was a paradoxical trend towards increased number of AF episodes while on the drug, this was offset by significantly decreased episode durations, which resulted in a decreased overall burden. There were no substantial effects on the QT or QRS intervals, and the most common side effect was gastrointestinal intolerance, which resulted in one patient withdrawal. Thyroid stimulating hormone (TSH) values did rise in some patients, but with no clinical effect. Thus, the authors concluded that ATI-2042 is a safe, well-tolerated drug with a promising efficacy against AF.

In spite of the small size of this study, the results are indeed promising. At the maximum dose of ATI-2042, there was an 87% relative risk reduction in the AF burden. Unfortunately, the study does not comment on how symptomatic the patients were pre- and post-drug and thus, the implications for patient quality of life must be assumed. ATI-2040 also did not have any significant effects on the QT interval in this study, nor were there any proarrhythmic events. While this is promising data, it must be contrasted with earlier animal data that demonstrated QT prolongation with ATI-2040.[16] Bear in mind that all of the patients in this study had pacemakers and intermittent/continuous pacing may have impacted favourably on the QT interval. Otherwise, the authors should be commended on their choice to study the drug's efficacy on a population of patients with permanent pacemakers. An implanted device is the most comprehensive way to assess for AF burden, and it is already known that longer durations of monitoring are superior for detecting AF than intermittent monitoring.[17] Furthermore, as the authors point out, using time to first AF recurrence does not take into account that AF episodes may cluster and thus, the endpoint may not accurately assess the reduction of AF over time. The main limitation of the pacemaker approach used in this study is the difficulty in comparing the efficacy of ATI-2040 to amiodarone or other antiarrhythmic agents given the dearth of pacemaker data available for those agents. Ideally, the efficacy could have been compared with an alternative antiarrhythmic in a separate study period. Pacemakers are also not perfect, with about 11% of the episodes logged in this study being due to inappropriate atrial over- or under-sensing by the device.

This small study also introduces a number of questions which have yet to be answered before ATI-2040 can be applied on a broader scale. First, the drug has potentially toxic effects on canine testicular tissue, which is why the study excluded males and non-sterile females from this study. Obviously, this is an important limitation and according to the authors, will be the subject of further study. Gastrointestinal side effects were another concern, causing one patient withdrawal out of only six patients. The TSH was also observed to rise in half of the patients within just 8 weeks. While the authors stated that these abnormalities did not result in any clinical manifestations, such a rise over a relatively short period of time raises the concern of thyroid effects over the long term.

Despite these limitations, the study of Arya *et al.* makes an important contribution to the literature and in the ongoing development of novel antiarrhythmic agents. Ideally, a prospective, comparative study of ATI-2040 against a conventional drug such as amiodarone in a larger cohort of patients will be needed before any definitive comments can be made about the drug. Pending further results, we can only hope that ATI-2040 or some other agent shall provide the efficacy of amiodarone without its toxicity, and in so doing, end our ongoing search for that Holy Grail.

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