Rethinking the reasons to treat atrial fibrillation? The role of dronedarone in reducing cardiovascular hospitalizations

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The management of patients with atrial fibrillation has changed considerably over the past decade, largely because of data derived from clinical trials. Although studies comparing strategies of rate control vs. rhythm control consistently failed to demonstrate the benefit of a rhythm control strategy, to argue that rhythm control is of no value to argue with imprecision. AFFIRM, the largest of the rate vs. rhythm trials, showed, in multivariate analysis, that those patients who stayed in sinus rhythm had a reduced mortality, although this was offset by the use of antiarrhythmic drugs.1 In contrast, although no benefit of a rhythm control strategy was found in the AF-CHF study (in which all patients had left ventricular dysfunction and the predominant antiarrhythmic drug used was amiodarone), there was also no trend towards increased mortality with the use of antiarrhythmic therapy.2 Despite negative outcomes in terms of mortality, rhythm control does have some benefits. Analyses of patients who were able to maintain sinus rhythm (as opposed to being randomized to a rhythm control strategy regardless of outcome) does appear to show a benefit of rhythm control, at least in terms of quality of life.3 In addition, there are many patients with atrial fibrillation in whom the arrhythmia is clearly associated with unpleasant or intolerable symptoms and these patients benefit symptomatically from restoration of sinus rhythm. Antiarrhythmic drugs remain problematic, however, given their side effects and propensity for significant proarrhythmia.

Until recently, clinical trials of antiarrhythmic drugs in patients with atrial fibrillation concentrated on suppression of the arrhythmia as determined by freedom from atrial fibrillation at a predetermined endpoint (usually 1 year or less) or by measuring time to first symptomatic recurrence. Data from antiarrhythmic trials that utilize daily transtelephonic monitoring and from interrogation of permanent pacemakers reveal a high prevalence of asymptomatic atrial fibrillation and demonstrate the weakness of using symptomatic arrhythmia recurrences as an endpoint.4,5 Not only does a primary endpoint of symptomatic arrhythmia recurrence fail to capture asymptomatic episodes, but the design of such trials often includes withdrawal of study drug once recurrence has been documented. If antiarrhythmic drugs are stopped at this point, it becomes difficult to address the long-term safety of these agents and precludes the use of additional potential endpoints.

Mortality is a difficult sole primary endpoint in trials of atrial fibrillation, as annual mortality is relatively low and highly dependent on the cause of the arrhythmia. Nevertheless, it is a vital measurement to address. Professional societies on both sides of the Atlantic have recently considered the problems of trials of drugs in atrial fibrillation and have suggested that additional endpoints may be valuable in the assessment of these agents.6,7 These include the reduction in outcomes of atrial fibrillation such as mortality, hospitalization, and stroke, as well as economic factors such as the cost of treatment. The ATHENA trial, which compared the atrial antiarrhythmic agent dronedarone to placebo in the treatment of atrial fibrillation, was designed with these aspects in mind.8 Based in large part on the ATHENA results, dronedarone was approved this summer by regulatory agencies in North America and it has subsequently been released in the USA with the unique indication of reducing the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial flutter or fibrillation. The trial is named after a Greek goddess, born, fully formed, and clothed in armour, from Zeus’s head. Does this trial, the largest published antiarrhythmic study, provide new and definitive data specific to dronedarone, or are there chinks in Athena’s armour which leave the results vulnerable to interpretation?

In the ATHENA trial, patients were kept on the assigned therapy (dronedarone or placebo) for at least 1 year of follow-up, regardless of whether or not atrial fibrillation recurred, and the combined endpoint consisted of a first hospitalization for a cardiovascular...
event or death from any cause. ATHENA demonstrated that the use of dronedarone among patients with atrial fibrillation, who had been in sinus rhythm for some period in the preceding 6 months and who had one or more risk factors for stroke, was associated with a decreased combined endpoint when compared with patients treated with placebo. The overall death rate did not differ between the two groups, although there was a statistically significant lower death rate due to cardiovascular causes in the dronedarone group. This is the first trial of an atrial antiarrhythmic agent to demonstrate a reduction in a primary endpoint other than recurrence of atrial fibrillation and these important results raise the question as to whether this may be a specific effect of dronedarone or whether a similar result might have been found in trials of other atrial antiarrhythmic drugs had they been large enough and had a similar primary endpoint been chosen. Furthermore, one has to question the clinical significance of cardiovascular hospitalization in this population. Is a reduction in hospitalizations a meaningful endpoint, or does it simply reflect a decrease in a minor nuisance?

Based on an analysis of data from the AFFIRM study which showed that patients hospitalized with atrial fibrillation had a higher risk of death in the next several years, Wyse et al. argued that a surrogate endpoint that includes hospitalization is indeed an appropriate endpoint for therapy in trials of atrial fibrillation. While this may be true, the European guidelines for endpoints in atrial fibrillation trials caution that hospitalization should be divided into admissions for atrial fibrillation recurrence and all other admissions. In the ATHENA trial, the excess of first hospitalizations for cardiovascular events was driven by recurrent atrial fibrillation. Although this is an important outcome, it is conceivable that many patients hospitalized with recurrent atrial fibrillation could have been managed on an outpatient basis, raising the question of the clinical significance of such an endpoint. A more intriguing finding was the observation that there was a decrease in the number of patients hospitalized for an acute coronary syndrome. Could this be a chance finding or might dronedarone have an anti-ischaemic effect perhaps explained by its inhibitory effect on inward calcium current or the slow sodium current, its non-specific anti-adrenergic effect, the reduction of atrial fibrillation episodes, the reduction of heart rate during recurrent episodes of arrhythmia or an effect on coronary vasodilation?

The answer will have to await more detailed analysis.

Is the ATHENA study unique in its findings? From the perspective of a predetermined primary endpoint it is. But this does not mean that similar findings have not been reported before with other antiarrhythmic agents. The DIAMOND trial studied 1518 patients with severe left ventricular dysfunction and symptomatic congestive heart failure, half of whom were randomized to dofetilide and the remainder to placebo. Approximately 40% of each group had documented atrial fibrillation. Although there was no difference in mortality between the two groups, patients with atrial fibrillation randomized to dofetilide were more likely to convert to sinus rhythm and less likely to have recurrent arrhythmia. While not a primary endpoint of the study, secondary analysis showed that dofetilide reduced the risk of hospitalization for worsening heart failure, a phenomenon predominantly seen in the group with atrial fibrillation. Although the patients in the DIAMOND study are not directly comparable to those in the ATHENA study, the effect on hospitalization was similar in the two studies. Of note, patients in the DIAMOND study had more severe heart disease than those in ATHENA and were more similar to the ANDROMEDA study patients, a clinical trial in which dronedarone, prescribed for patients with severe congestive heart failure, was associated with an apparent increase in cardiac mortality. It has been suggested that the excess ANDROMEDA mortality might have been related to inappropriate withdrawal of ACE inhibitors in the dronedarone-treated group because of a drug-induced increase in creatinine levels. This hypothesis has not, however, been proved, and comparison of ANDROMEDA and ATHENA raises the spectrum of a dual effect of dronedarone, namely, the potential for increasing mortality among patients with recently decompensated, severe and unstable heart failure but a neutral mortality effect and decreased first hospitalization among patients with atrial fibrillation and no more than moderate heart failure.

What then does the ATHENA trial tell us about the treatment of atrial fibrillation in general and the role of dronedarone in particular? It demonstrates the safety of dronedarone in a population of patients with paroxysmal atrial fibrillation or recent onset persistent atrial fibrillation and a moderate to high risk of stroke, excluding those with severe heart failure. It also demonstrates that the drug can reduce hospitalizations, an effect that it is both economically valuable and which is presumably of benefit to patients. ATHENA does not tell us whether any of these effects are dronedarone-specific nor does it tell us whether an antiarrhythmic agent with a greater efficacy would have a greater effect in reducing hospitalizations. Nevertheless, modern clinical practice is driven by well-designed clinical trials and the ATHENA trial is a large, well-powered study which successfully achieved its primary endpoint. There are certainly large numbers of patients who match the entry criteria for the ATHENA trial, in which dronedarone was clearly shown to be safe and relatively effective. Dronedarone will clearly have a role in the treatment of atrial fibrillation and the clinician, using it in carefully selected patients who match those in the ATHENA study, can feel confident that it is a relatively safe agent which may be started in the outpatient setting and which has been shown to have beneficial effects on patient outcome over and above the usual parameters studied in patients with this arrhythmia. Whether or not the beneficial effects of dronedarone on cardiovascular hospitalization shown in the ATHENA trial are unique to dronedarone is unproven, but the burden of proof now lies with the manufacturers of other atrial antiarrhythmic agents.

References


Acute myocardial infarction and cardiogenic shock caused by a mobile thrombus in the ascending aorta unassociated with atherosclerosis

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A 78-year-old woman with a history of heavy watery diarrhoea 9 days prior, presented with chest pain, suggesting an ongoing myocardial infarction. Transthoracic echocardiography revealed inferior wall and right ventricular akinesia. In addition, it revealed an unidentified floating mass in the aortic wall above the aortic valve but no intracardiac thrombus or pathological findings. Contrast-enhanced computed tomography revealed the presence of a pedunculated floating mass in the right coronary sinus of Valsalva. Intraoperatively, a 4 × 3 cm diameter mobile thrombus was observed to be attached to the aortic wall above the right leaflet of the aortic valve and had lodged into the right coronary ostium (Panels A and B). The coagulation examination findings were normal. Because these features were suggestive of an aortic thrombus obstructing the right coronary ostium, the mass was surgically resected. We did not perform angiography before the surgery because we feared that it might cause an occlusion of the distal right coronary artery (RCA) or cerebral artery embolization. Intraoperatively, a 4 × 3 cm diameter mobile thrombus was observed to be attached to the aortic wall above the right leaflet of the aortic valve and had lodged into the right coronary ostium (Panels C and D). Microscopically, the mass was determined to be a mixed thrombus containing mostly of fibrin, erythrocytes, platelets, and neutrophils and indicated that the formation of the thrombus was 7–8 days old (Panel E). Although she had neither atrial fibrillation (AF) during hospitalization, a history of arrhythmias, nor episodes of palpitations, possible speculation was that the AF episodes during an electrolyte/fluid imbalance promoted the thrombus formation, which embolized into the sinus of Valsalva and drifted with the blood flow into the RCA ostium.

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