Dronedarone: an alternate choice to sotalol and amiodarone in the treatment of atrial fibrillation/flutter in patients who have coronary heart disease

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This editorial refers to the ‘Effect of dronedarone on clinical end points in patients with atrial fibrillation and coronary heart disease: insights from the ATHENA trial’ by R. Pisters et al., on page 174.

A large number of patients with atrial fibrillation (AF) have coronary heart disease (CHD) or concomitant risk factors. In ATHENA (A placebo controlled, double blind Trial to assess the efficacy of dronedarone for the prevention of cardiovascular Hospitalization or death from any cause in patients with Atrial fibrillation and flutter), 30% of the patients had CHD.1 The results of the CAST (Cardiac Arrhythmia Suppression Trial)2 led physicians to carefully select antiarrhythmic drugs that can be used safely in the CHD population. The clinical trials have demonstrated neutral mortality risk in CHD patients treated with sotalol, amiodarone, dofetilide, and most recently dronedarone.1,3 – 6 Based on these data, these drugs have been recommended by the guidelines for use in the CHD population.7 – 9 Dofetilide is only available in the USA and not included in the ESC guidelines. Thus, physicians in most countries only have sotalol, amiodarone, and dronedarone as therapeutic options for the treatment of AF in patients with CHD. Owing to the over-prescribing of amiodarone and its potential adverse effects, the revised guidelines downgraded amiodarone as a second choice in many patient subgroups with AF.7,8 The results of the PALLAS (Permanent Atrial fibrillation Ligation outcome Study using dronedarone on top of standard therapy)9 raised concerns of adverse outcomes with dronedarone in patients with permanent AF and this concern diminished some of the enthusiasm for using dronedarone as a front-line alternative to amiodarone.

The ATHENA trial demonstrated that dronedarone significantly reduced cardiovascular hospitalization and death.1 ATHENA was the largest antiarrhythmic drug trial in AF/atrial flutter (4628 patients) ever performed. The explanation of this benefit has puzzled clinicians since other drugs, like amiodarone, have not been able to demonstrate this beneficial effect. An overlooked finding of the ATHENA was the 30% reduction of cardiovascular hospitalization secondary to acute coronary syndromes (ACS).1,11 This outcome suggested the possible benefit and safety of dronedarone use in a CHD population.

In a post hoc analysis of the CHD patients in the ATHENA published in this issue of the Journal, Pisters et al.12 stated that some of dronedarone’s benefits in a substudy of 1405 patients followed for 2.5 years. The primary outcome (cardiovascular hospitalization or death) occurred in 47% of the placebo compared with 38% of the dronedarone population. This 27% relative risk reduction in the primary endpoint was statistically significant (P = 0.0002) and consistent with the overall ATHENA findings (24% decrease). In addition, dronedarone reduced the number of first ACS events by 33% compared with the placebo (P = 0.04).

The mechanism of these beneficial findings has not been well-studied. Dronedarone, similar to amiodarone, is a coronary artery dilator, slows the heart rate, and has a low risk of ventricular proarrhythmia. Dronedarone causes coronary vasodilatation that is refractory to the inhibition of the nitric oxide synthase pathway while amiodarone has coronary vasodilatation highly dependent on this pathway.13 In vitro studies demonstrate that dronedarone is a more potent inhibitor of the slow L-type calcium channels when compared with amiodarone.14 Dronedarone is an antagonist of the α- and β-adrenoreceptors and thus exhibits Class II activity,15 but has less β-1 adrenoreceptor antagonistic effect compared with amiodarone. Multiple basic science studies have demonstrated that dronedarone suppresses ischaemia-induced and reperfusion ventricular arrhythmias.16 – 19 It is unclear if any of these mechanisms explain the safety of dronedarone in CHD. Pisters et al.12 stated that whilst the underlying mechanism of action is unclear, dronedarone appears to prevent the occurrence of microcirculatory abnormalities in the ventricles during AF. The alleviation of these abnormalities, which appear to represent early changes in the myocardial structure of AF patients, suggests that dronedarone might be particularly effective in the early stages of the disease.6

Some of dronedarone’s benefits might partially be explained by its ability to decrease systolic and diastolic blood pressure by...
2–3 mmHg compared with the placebo and amiodarone or through some other properties including heart rate slowing, coronary vasodilatation, or properties that are yet to be determined. The mechanisms causing this blood pressure lowering are not completely understood. If the blood pressure lowering or the reduction in the pressure rate product explains some of the beneficial outcomes or reduces the demand ischaemia remains speculative.

How do these findings affect how the clinician practices? Although less efficacious than amiodarone in the prevention of recurrent AF, dronedarone appears to be a safer, well-tolerated drug in patients with preserved left ventricular function.20,21 Dronedarone can be considered as an alternative therapy to amiodarone especially in younger patients and for those who have developed end-organ toxicity from amiodarone. Both amiodarone and dronedarone reduce the risk of proarrhythmia and torsade de pointes compared with sotalol, especially in patients with ventricular hypertrophy. In the rhythm control arm of both the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and the AF-CHF (Atrial Fibrillation and Congestive Heart Failure) trials, with 62 and 82% amiodarone use, respectively, there were statistically higher rates of cardiovascular hospitalizations,22,23 The AFFIRM study findings were recently highlighted in a retrospective analysis by Saksena et al.24 The high re-hospitalization rates were counterintuitive given a higher efficacy of amiodarone in suppressing the AF recurrences in the DIONYSOS [randomized Double blind trial to evaluate efficacy and safety of drOne Darone (400 mg b.i.d.) versus amiDARone (600 mg q.d. for 28 daYS, then 200 mg qd thereafter) for at least 6 mOnths for the preven?tion of Sinus rhythm in patients with atrial fibrillation].20 Naccarelli et al.25 reported that the healthcare costs associated with cardiovascular hospitalizations and inpatient deaths among ATHENA-like patients in the USA are high, with a mean of $10 908 per non-fatal admission. Over a 1-year period, 53.9% of these patients had a cardiovascular hospitalization. Thus, a reduction in cardiovascular control arm of both the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) and the AF-CHF (Atrial Fibrillation and Congestive Heart Failure) trials, with 62 and 82% amiodarone use, respectively, there were statistically higher rates of cardiovascular hospitalizations,22,23 The AFFIRM study findings were recently highlighted in a retrospective analysis by Saksena et al.24 The high re-hospitalization rates were counterintuitive given a higher efficacy of amiodarone in suppressing the AF recurrences in the DIONYSOS [randomized Double blind trial to evaluate efficacy and safety of drOne Darone (400 mg b.i.d.) versus amiDARone (600 mg q.d. for 28 daYS, then 200 mg qd thereafter) for at least 6 mOnths for the preven?tion of Sinus rhythm in patients with atrial fibrillation].20 Naccarelli et al.25 reported that the healthcare costs associated with cardiovascular hospitalizations and inpatient deaths among ATHENA-like patients in the USA are high, with a mean of $10 908 per non-fatal admission. Over a 1-year period, 53.9% of these patients had a cardiovascular hospitalization. Thus, a reduction in cardiovascular hospitalization in this population, by therapies such as dronedarone, would be expected to reduce the healthcare costs.

Two cases of severe hepatocellular liver injury leading to acute liver failure requiring transplant, led to new regulatory labelling of the drug which was more restricting in Europe than the USA.26 Over 1 000 000 patients have been exposed to dronedarone worldwide and this issue seems to have been minimized with no new major reported cases. In the USA, we obtain a baseline liver function test, periodically monitor liver function, and obviously avoid the use of the drug in patients with advanced liver disease.

Should dronedarone be used as an additional treatment to prevent ACS? Although Pister et al.12 reported that dronedarone reduced the ACS events by 33% with the most benefit in patients with depressed left ventricular ejection fractions, the authors do not advocate dronedarone as an anti-ACS therapy and I agree. Until there are more data from the carefully performed trials, the main message of this study is that dronedarone is safe when properly used in non-permanent AF patients with CHD. Patients with or at risk of CHD should still be treated with other standard preventative measures. Sotalol, dronedarone, and amiodarone all slowed heart rate in addition to beta-blockade and appropriate adjustment of beta-blocking doses may be needed. However, as demonstrated with amiodarone in the post-myocardial infarction trials, beta-blockers should be continued4,5 because of their added benefit on survival.

Similar to amiodarone, dronedarone interacts with the commonly prescribed drugs used in CHD patients such as metoprolol and simvastatin.27 Dronedarone can increase serum simvastatin levels two- to four-fold and thus promote statin-induced myalgia. It has been recommended that the simvastatin doses should be low (10 mg a day) in patients taking simvastatin in combination with amiodarone. Simvastatin doses probably should be no higher than 10–40 mg a day when used in conjunction with dronedarone. Since the dronedarone–ranolazine interactions with atorvastatin and rosuvastatin are less marked, and there is no significant interaction with pravastatin, these lipid-lowering agents are safer to use in combination with dronedarone. Metoprolol and dronedarone interact via a CYP2D6 inhibition that results in an increased bioavailability of metoprolol.28

Dronedarone should be avoided in patients with advanced congestive heart failure with or without CHD.29 The majority of the patients enrolled in the ATHENA had normal or low normal left ventricular ejection fraction. An ejection fraction of <45% was only present in 11.3% of the patients in the dronedarone group and 12.5% in the placebo group. A history of congestive heart failure, New York Heart Association (NYHA) Class II or III was present only in 20% in the dronedarone group and 22% in the placebo group. An interesting finding of the post hoc analysis12 is that patients with a left ventricular ejection fraction of <35% actually had a 33% decrease in the ACS events.

Are there any new data that might alter the above recommendations? The basic science studies suggest that dronedarone is less effective than amiodarone in suppressing AF.30 However, the same investigators noted that the addition of ranolazine, an anti-anginal agent, to dronedarone added significant efficacy to either drug alone.31 The HARMONY (A Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in Combination in Patients With Paroxysmal Atrial Fibrillation) trial is currently enrolling patients and studying if this combination may lead to a safe and more effective combination antiarrhythmic drug. This combination will be of major importance to the AF patient with CHD.32

Dronedarone remains a first-line therapy for many patients with AF/atrial flutter. The highest benefit and the lowest risk patients appear to be those with structural heart disease, who have a preserved ejection fraction and no recent decompensated heart failure. Although it is less efficacious than amiodarone in maintaining sinus rhythm, its effectiveness is similar to the other antiarrhythmic drugs used to treat AF. Based on the ANDROMEDA (A Study to Evaluate the Effect of Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating morbidity Decrease), dronedarone should not be used in CHD patients with heart failure NYHA Class III–IV and left ventricular systolic dysfunction. Whether the combination of dronedarone–ranolazine will play a role in AF patients with CHD will be determined by the results of the trials studying this combination agent.

Conflict of interest: G.V.N. is a consultant and on the steering committee for Sanofi.

References