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EDITORIAL

Dronedarone: the Hope and the Hype

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Atrial fibrillation (AF) is the commonest cardiac arrhythmia afflicting ~1% of the total population in an age-dependent manner with 2.3% of individuals older than 40 years of age, or 5.9% of people older than 65.[1] Approximately 70% of persons with AF are between 65 and 85 years of age. Patients with AF experience significantly higher mortality rates than patients without AF; adjusted relative mortality risk has been found approximately 20% higher in patients with AF in all age-sex strata during each of the 3 years studied ($P < 0.05$).[2] One sixth of all strokes are attributable to AF and the percentage of strokes due to AF increases dramatically with age; of course the risk of stroke is significantly decreased with anticoagulation therapy by 60-70%, but this has its own inherent problems. Unfortunately, the use of antiarrhythmic drugs (AADs) employed thus far to maintain sinus rhythm is severely problematic with treatment being occasionally worse than the disease. Nevertheless, the goal is still to maintain sinus rhythm, since teleologically this is the optimal rhythm man is born and should live with, but the means to effect and sustain this, have inherent potentially prohibitive risks, as shown in the AFFIRM, RACE and other trials.[3-5] However, even in the AFFIRM trial, which showed that AADs may be associated with increased mortality, overall maintenance of sinus rhythm (with or without AADs) was associated with improved survival compared with persistent AF. This observation supports the long-recognized mortality risk associated with AF,[2] and hence the continued quest for development of new and safer antiarrhythmic agents and methods to maintain sinus rhythm. In this endeavor, newer pharmacological agents have recently emerged but not yet fulfilled this expectation. Among them, *dronedarone*, a modified molecule of amiodarone devoid of the iodine moiety, was heralded as the agent with the new hope.[6]

In the initial studies employing the new drug (**EURIDIS** & **ADONIS**),[7] dronedarone was significantly more effective than placebo in maintaining sinus rhythm in patients with paroxysmal AF (Table 1). Even, in patients with persistent or permanent AF, the new drug was reported to have favorable effects.[8,9] However, when compared with amiodarone in patients with persistent AF (**DIONYSOS** study), dronedarone was less effective than amiodarone in decreasing AF recurrence, but the authors claimed that the new drug had a better safety profile, [10] but the follow-up was limited to a median treatment duration of 7 months. The first worrisome outcome from this new AAD came from the **ANDROMEDA** trial,[11] which was terminated early because of a higher rate of death with dronedarone. This study was conducted in patients with symptomatic congestive heart failure, a left ventricular ejection fraction of $\leq$35%, and recent hospitalization with new or worsening heart failure.

Table 1. Dronedarone Studies

Study	No. of Patients	Study Population	Primary Endpoint	Follow-up	Results
DAFNE	199	Patients with persistent AF scheduled for cardioversion	Time to AF relapse	6 mos	Median time to first AF recurrence: 5.3 days in the placebo group, & 60 days in the dronedarone 800 mg group (relative risk reduction 55%; *P*=0.001)
EURIDIS /ADONIS	1237 (828 dronedarone / 409 placebo)	Patients with paroxysmal AF	Time to AF recurrence	12 mos	Median times to AF recurrence: 41 days in placebo group & 96 days in dronedarone group (P= 0.01) (European trial); respective durations in the non-European trial: 59 & 158 days (P= 0.002)
ERATO	174 (85 dronedarone / 89 placebo)	Patients with permanent AF	Mean ventricular rate on day 14 (by Holter)	6 mos	Reduction of 11.7 bpm (P <0.0001) sustained at 6 months
ANDROMEDA	627 (310 dronedarone / 317 placebo)	Patients with HF (NYHA III/IV), LVEF ≤35%	Death from any cause or hospitalization for heart failure	2 mos	25 deaths in the dronedarone group (8.1%) & 12 in the placebo group (3.8%) (hazard ratio-HR, 2.13; P = 0.03).
ATHENA	4628 (2301 dronedarone / 2327 placebo)	Patients with paroxysmal or persistent AF or flutter	first hospitaliza-tion due to CV events or death	21 mos	24% reduction in death from all causes or first hospitalization for a CV event
DIONYSOS	504 (249 dronedarone / 255 amiodarone)	Patients with persistent AF	AF recurrence	7 mos	AF recurrence was higher with dronedarone compared with amiodarone (63.5 vs 42.0%) (HR 1.59; P<0.0001)
PALLAS	3149 (1572 dronedarone / 1577 placebo)	Patients with permanent AF	Stroke, MI, systemic embolism, or CV death or unplanned hospitalization or death	3.5 mos	16 (1%) deaths in the drug vs 7 (0.4%) in the placebo group. CV death, MI, stroke or systemic embolism in 32 (2%) vs 14 (0.9%) respectively (hazard ratio 2.3; p=0.009)

AF = atrial fibrillation; CV = cardiovascular; HF = heart failure; HR = hazard ratio; MI = myocardial infarction; mos = months; NYHA = New York Heart Association

There followed **ATHENA**, a prospective, double-blind study,[12] assessing morbidity and mortality rates in 4,628 patients with AF or atrial flutter and at least one other cardiovascular risk factor. This study excluded patients with decompensated heart failure. It showed that dronedarone, added to standard therapy, significantly reduced the risk of a first cardiovascular hospitalization or death by 24% in patients with AF or atrial flutter.

Although, with the results of the ATHENA trial, it seemed that a small niche was established for dronedarone for patients with paroxysmal or persistent AF or flutter, for prevention of AF recurrences, or even reduction of hospitalizations due to cardiovascular events, at least before resorting to amiodarone, as long as they had no symptoms of congestive heart failure or low ejection fraction, there followed shortly the results of the PALLAS trial, which cast serious doubts about the overall safety of this agent.[13,14] With regards to safety of the drug, even before this latter trial, it should be noted that the adverse events occurred significantly more frequently with dronedarone than with placebo and included bradycardia, QT-interval prolongation, diarrhea, nausea, rash, and an increase in the serum creatinine level. In patients of the ATHENA trial, no significant increase in the rates of thyroid or pulmonary disorders was seen with dronedarone, however, as the authors noted, the mean follow-up for patients in the trial was only 21 months and many patients treated with amiodarone have such side effects (especially pulmonary fibrosis) later than 2 years after initiating therapy. Furthermore, a major clue for limited tolerance of the drug in this trial was the very high rate of premature discontinuation of the study drug reaching at 30.2% in the

dronedarone group. Subsequently, alarming news arrived about the potential liver toxicity of the drug from an FDA drug safety communication. In January 2011, the FDA warned "healthcare professionals and patients about cases of rare, but severe liver injury, including two cases of acute liver failure leading to liver transplant in patients treated with the heart medication dronedarone (Multaq)" (http://www.fda.gov/drugs/drugsafety/ucm240011.htm).[15]

The Permanent Atrial fibriLLAtion Outcome Study Using Dronedarone on Top of Standard Therapy (**PALLAS**) study, sponsored by the drug maker, was being conducted to assess the potential clinical benefit of dronedarone in patients over 65 years of age with permanent AF. PALLAS was launched in July 2010 and was designed to enroll 10,800 patients, with an estimated completion date of August 2013, but was stopped prematurely in July 2011 due to doubling of the mortality rate in this cohort (http://www.theheart.org/article/1251405.do).[13,14] Only 3149 patients had been enrolled at the time the study was stopped. As of June 30, 2011, 16 (1%) patients had died in the drug group compared to 7 (0.4%) patients dying in the placebo group. Cardiovascular death, myocardial infarction, stroke or systemic embolism had occurred in 32 (2%) patients receiving the drug vs 14 (0.9%) among those receiving placebo (hazard ratio 2.3; p=0.009). On July 21, 2011, the FDA issued a warning that "healthcare professionals should not prescribe Multaq to patients with permanent atrial fibrillation" (http://www.fda.gov/Drugs/DrugSafety/ucm264059.htm).[14]

Thus, based on all these developments regarding this new agent, it seems that there may only remain a possible indication of this drug in patients with paroxysmal or persistent AF with preserved left ventricular function and no symptoms or signs of heart failure, while it is contraindicated in patients with permanent AF, regardless of the left ventricular function status. However, as post-drug surveillance has already revealed worrisome problems with potential severe liver toxicity, taken altogether, it seems prudent to remain very circumspect in prescribing this medication in any patient, until further long-term data are available. It is also apparent that regulatory authorities have been a bit hasty, to say the least, with regards to their endorsement of this agent before all information had become available. It also remains inexplicable why the drugmaker and the involved investigators ever thought that the drug would have an indication in patients with permanent AF; nevertheless their action provided important negative information that will prevent future problems lest some physicians would have proceeded to prescribe this medication in such a high-risk patient group.

REFERENCES

1. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med* 1995; 155: 469-473.
2. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. *Arch Intern Med* 1998; 158: 229–234.
3. Wyse DG, Waldo AL, DiMarco JP, et al; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002; 347:1825–1833.
4. The AFFIRM Investigators. Relationships between sinus rhythm, treatment, and survival in the AFFIRM study. *Circulation* 2004; 109:1509–1513.
5. Van Gelder IC, Groenveld HF, Crijns HJ, et al; RACE II Investigators. Lenient versus strict rate control in patients with atrial fibrillation. N Engl J Med 2010; 362:1363–1373.
6. Connolly SJ, Hohnloser SH. Dronedarone for atrial fibrillation. *J Am Coll Cardiol* 2010;56:16, 1353-1354.
7. Singh BN, Connolly SJ, Crijns HJGM; EURIDIS & ADONIS Investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007;357:987-999.
8. Touboul P, Brugada J, Capucci A, Crijns HJ, Edvardsson N, Hohnloser SH. Dronedarone for prevention of atrial fibrillation: a dose-ranging study. *Eur Heart J* 2003;24:1481-1487.
9. Davy J-M, Herold M, Hoglund C, et al for the ERATO Study Investigators Dronedarone for the control of ventricular rate in permanent atrial fibrillation: The Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation (ERATO) study. *Am Heart J* 2008;156:527.e1-527.
10. Le Heuzey JY, De Ferrari GM, Radzik D, Santini M, Zhu J, Davy JM. A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: the DIONYSOS study. *J Cardiovasc Electrophysiol* 2010;21:597-605.
11. Kober L, Torp-Pedersen C, McMurray JJ; Dronedarone Study Group. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008; 358:2678–2687.
12. Hohnloser SH, Crijns HJ, van Eickels M; ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009; 360:668–678.
13. http://www.theheart.org/article/1255799.do / http://www.theheart.org/article/1251405.do
14. http://www.fda.gov/Drugs/DrugSafety/ucm264059.htm
15. http://www.fda.gov/drugs/drugsafety/ucm240011.htm