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ArrhythmiaNEWS

From the Al-Sabah Arrhythmia Institute at St. Luke's-Roosevelt Hospital Center

Arrhythmia News is a physician bulletin providing information on arrhythmia services at **St. Luke's-Roosevelt Hospital Center** which may benefit you and your patients.

**10th ANNUAL
New Frontiers in Heart
Failure Therapy**
*Integrating Devices and
Pharmacotherapy*
Saturday, January 23, 2010
7:30 am - 4:30 pm
The Waldorf=Astoria Hotel
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Introduction of Dronedaron

Amiodarone has been the most widely used antiarrhythmic drug for the treatment of atrial fibrillation (AF). Its low proarrhythmic risk allowing initiation on an outpatient basis and potency made it an attractive first-line choice. However, the high incidence of potentially serious extracardiac side effects often lead to reluctance from both physicians and patients to use it long-term.

In response an active effort was made to identify a "safe amiodarone" and ultimately dronedarone was developed. Dronedaron is structurally closely related to amiodarone, but does not contain the iodine components, which are thought to be responsible for most of amiodarone's toxicity. Like amiodarone, dronedaron exhibits multi-channel (Na⁺, K⁺ and Ca⁺⁺) blocking properties as well as beta receptor antagonism.

Several studies, most carrying names from Greek mythology, have been conducted: **ERATO1**, **EURIDIS** and **ADONIS2** were the first smaller dronedaron trials, all demonstrating superior rhythm control

(reducing AF recurrence by ~25%) compared to placebo. Dronedaron also provided rate control, reducing ventricular rates during atrial fibrillation, as well as resting sinus rates, compared to placebo. The main side effects of dronedaron were gastro-intestinal, without a significant increase in serious side effects usually associated with amiodarone including thyroid, pulmonary, hepatic, neurologic and dermatologic.

Following these, the larger **ANDROMEDA** trial was initiated in patients with advanced heart failure. This phase III trial evaluated the efficacy and safety of dronedaron in patients hospitalized with symptomatic congestive heart failure and LVEF ≤35%, compared to placebo. Eligible patients were NYHA II-IV on admission with an episode of NYHA III-IV symptoms within one month. The trial was halted early due to a concerning excess mortality in the dronedaron arm in patients with NYHA class >II (HR 2.8) and/or LVEF <30% (HR 4.6).

Nevertheless, in July 2009 the FDA announced the approval of dronedaron for treatment of AF or atrial flutter in patients with associated cardiovascular risk factors, predominantly based on publication of the **ATHENA3** trial:

To determine the value of dronedaron in patients with AF, the **ATHENA** was performed. **ATHENA** was the largest antiarrhythmic trial ever conducted and enrolled over 4500 patients with moderate- to high-risk features, including age above 75 years or above 70 years with at least one cardiovascular risk factor such as hypertension, diabetes, prior stroke/TIA, left atrial enlargement, or an LVEF <40%. Patients were randomized to dronedaron (400 mg twice daily) or to placebo, in addition to chronic treatment with beta blockers, calcium-channel blockers, ACE inhibitors, or angiotensin-receptor blockers, digoxin, statins, and oral anticoagulation.

Besides a modest reduction in hospitalization for AF (21.9% vs 14.6%, HR 0.63), **dronedaron also reduced the risk of first cardiovascular hospitalization or death by**

24%, which is a first for an antiarrhythmic drug (see **Figure, next page**). This result was mainly driven by fewer admissions for AF and acute coronary syndromes. In contrast to **ANDROMEDA**, dronedaron did not lead to an excess in hospitalizations for heart failure in this study population, however only 29% of patients had a history of congestive heart failure, and 88% had a LVEF >45%. Other positive outcomes were a reduction in arrhythmic deaths and stroke.

Dronedaron vs amiodarone: The **DIONYSOS** trial was a short term (mean follow up: 7 months) randomized double-blind study comparing the efficacy and safety of dronedaron versus amiodarone in patients with persistent AF, in whom cardioversion and antiarrhythmic treatment were indicated. Atrial fibrillation after electrical cardioversion occurred in 36.5% of patients in the dronedaron arm vs. 24.3 % of patients in the amiodarone arm. Patients receiving dronedaron developed less thyroid and neurological events, as well as less premature study drug discontinuation due to any adverse events (13 in dronedaron arm vs 28 in amiodarone arm). In contrast, gastrointestinal events, consistent with prior studies, occurred more frequently in the dronedaron arm (32 vs 13). The **DIONYSOS** study was not designed to assess cardiovascular morbidity or mortality.

A recently published meta-analysis⁴ comparing the two drugs indirectly came to the conclusion that dronedaron has substantially less efficacy in maintaining sinus rhythm compared to amiodarone (amiodarone vs dronedaron: OR 0.49, 95% COI 0.37-0.63). However amiodarone was almost twice as likely to cause adverse events leading to drug withdrawal (OR 1.81, 95% COI 1.33-2.46), with an increase in overall mortality (OR 1.61, 95% COI 0.97-2.68) when compared to dronedaron. The above mentioned survival benefit of dronedaron over placebo could not be demonstrated (OR 0.86, 95% COI 0.66-1.11 vs placebo).

Dosing: Dronedaron (Multaq®) has been developed and is distributed by Sanofi Aventis. It is given as an oral fixed dose of 400 mg

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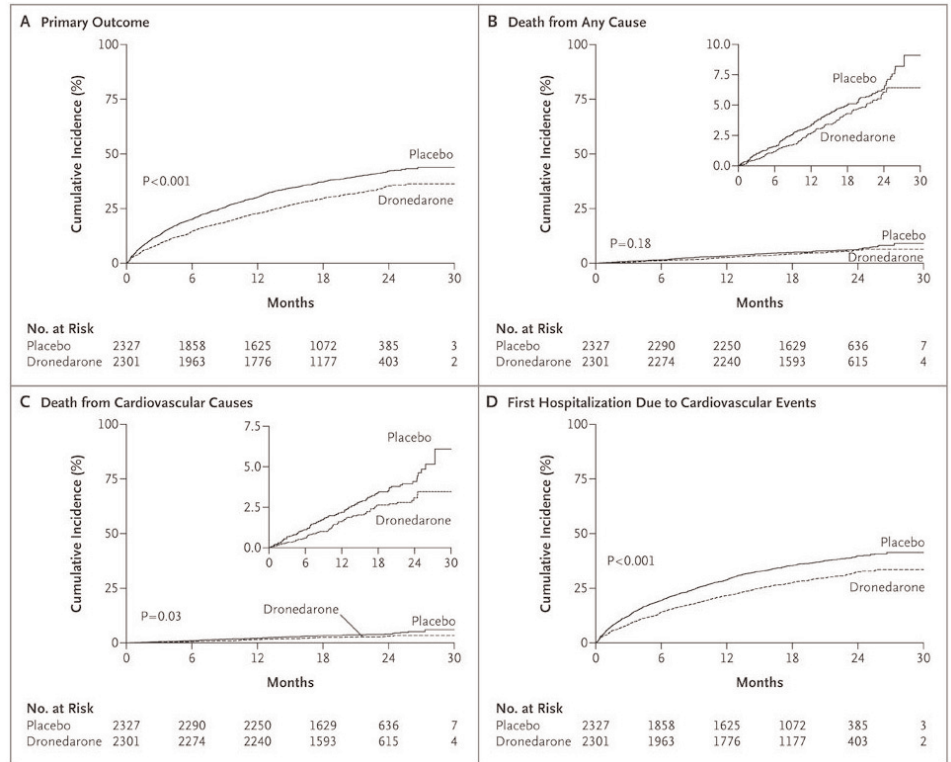
BID without need for loading, or adjustment in patients with renal or hepatic dysfunction. It is contraindicated in patients with NYHA class IV, and in those with NYHA class II and III with a recent (30 days) heart failure exacerbation.

Conclusion: Dronedaron is a weaker antiarrhythmic medication than amiodarone, but devoid of its extracardiac side effects. It can also serve as a rate control agent. Younger patients, in whom long-term toxicity of amiodarone is a concern, are most likely to be considered for dronedaron therapy. Gastro-intestinal side effects, especially diarrhea, occur in ~9% (compared to 6% with placebo), and have so far been the most commonly observed side effect prompting drug discontinuation. Thus dronedaron is a welcome addition to a limited antiarrhythmic arsenal but its role in clinical practice is as yet undefined and will require further study and comparison with other drugs and catheter ablation.

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Figure:



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