MÆDICA - a Journal of Clinical Medicine

JOURNAL CLUB

Dronedarone increases mortality in heart failure patients but might decrease mortality in patients with atrial fibrillation

Andrei Dumitru MARGULESCU, MD

Department of Cardiology, Emergency University Hospital, Bucharest, Romania

Heart failure is associated with an increased risk of sudden cardiac death due to malignant ventricular arrhythmias. Although treatment with class III (Vaugan Williams) antiarrhythmic drugs might decrease this risk, no such drug has proved effective in this setting. Amiodarone (a class III drug) has neutral effect on mortality in heart failure patients. This might be related to the frequent extracardiac adverse reactions of amiodarone (some of them severe) which might offset the benefits of this drug. Many of these adverse reactions are related to the iodine content of amiodarone. The hypothesis that dronedarone - a class III drug with similar electrophysiologic properties with amiodarone but without iodine content – might decrease mortality and morbidity in heart failure patients was tested in the ANDROMEDA trial (1). The study was conducted in 2002 but the results were only published this year. After the inclusion of 627 patients randomized 1:1 to receive either 400mg twice daily of dronedarone or placebo, the trial was stopped prematurely because of excess mortality in the active treatment group (8.1% vs. 3.8%; HR 2.13; 95% confidence interval [CI], 1.07 to 4.25; P = 0.03). The excess mortality was primarily related to worsening heart failure. The survival curve diverged very early; the mean follow-up of patients during the study was only 2 months. Thus, dronedarone should not be prescribed to patients with heart failure.

The question weather dronedarone is safe and improves outcome in patients with atrial fibrillation and additional risk factors was evaluated in the ATHENA study (2). Atrial fibrillation is frequently associated with heart failure; however, the ATHENA study excluded patients with NYHA class IV heart failure, while still recruited some patients with depressed left ventricular ejection fraction or mild to moderate heart failure. Preliminary results are encouraging (3), and it seems that dronedarone in this setting improves outcome, opposite to patients with manifest heart failure. Thus, dronaderone reduced the primary end-point of ATHENA study (time to first hospitalization + death from any cause) by 23% ($P < 0.001$) by decreasing both cardiovascular mortality (by 29%, $p = 0.03$), including arrhythmic death (by 45%, $p < 0.01$) and cardiovascular hospitalization (by 25%, $p < 0.001$).

Further studies are necessary to fully evaluate the role of dronedarone in the treatment of atrial fibrillation, the full spectrum of heart failure or both.

Comment on the papers:

1. **Kober L, Torp-Pedersen C, McMurray JJV, et al for the Dronedarone Study Group** – Increased Mortality after Dronedarone Therapy for Severe Heart Failure. *N Engl J Med* 2008; 358:2678-2687
2. **Hohnloser SH, Connolly SJ, Crijns HJ, et al** – Rationale and design of ATHENA: A placebo controlled, double-blind, parallel arm trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter. *J Cardiovasc Electrophysiol* 2008; 19:69-73
3. **Hohnloser SH** – A placebo-controlled, double-blind, parallel arm trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter (AF/AFL). *Heart Rhythm Soc*iety 2008 Scientific Sessions; May 15, 2008; San Francisco, CA. Abstract available at: http://www.hrsonline.org/News/Media/press-releases/athena_trial.cfm