Rate-Control vs Rhythm-Control for Atrial Fibrillation: A Controversy Reluctant to Die in the Era of Dronedarone?

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Abstract: Although restoring atrial fibrillation to sinus rhythm seems beneficial in patients with non-permanent AF, clinical trials have not observed any convincing benefit of a rhythm-control strategy compared with a rate-control strategy. This may be related with the adverse effects associated with antiarrhythmic drugs that may offset any beneficial effect of this approach.

Dronedarone has been recently approved for the treatment of patients with paroxysmal or persistent atrial fibrillation and is the only antiarrhythmic agent that has shown a benefit in the reduction of the incidence of hospitalization due to cardiovascular events or death compared with placebo.

As AFFIRM is the most relevant clinical trial that has suggested that rhythm and rate control rates strategies are similar, and ATHENA the most important study analyzing the effects of dronedarone in patients with atrial fibrillation, the results of both studies have been compared.

Keywords: Atrial fibrillation, antiarrhythmic drugs, dronedarone, AFFIRM, ATHENA.

TO THE EDITOR

Although restoring atrial fibrillation (AF) to sinus rhythm seems the best approach in patients with non-permanent AF, clinical trials such as AFFIRM showed in 4060 patients with AF and a high risk of stroke or death that rhythm-control strategy offered no survival advantage over the rate-control strategy. Moreover, hospitalizations and adverse drug effects were more frequent in those patients assigned to rhythm-control group [1]. However, an analysis of AFFIRM reported that sinus rhythm was an important determinant of survival, and that any beneficial effect of antiarrhythmic drugs was offset by their adverse effects [2]. After the publication of AFFIRM, many patients that would benefit from a rhythm control approach were not treated accordingly.

Dronedarone is an antiarrhythmic agent recently approved for the treatment of paroxysmal or persistent AF in different countries, and regions, including United States, Canada, or European Union. The ATHENA trial showed in 4,628 patients with AF who had additional risk factors for death that dronedarone reduced the incidence of hospitalization due to cardiovascular events or death compared with placebo [3]. However, PALLAS and ANDROMEDA trials showed that dronedarone was harmful in patients with permanent AF as well as in patients with heart failure and left ventricular systolic dysfunction, respectively [4, 5]. Moreover, as it has been suggested that dronedarone may be associated with severe hepatotoxicity, monitoring liver function is advisable in patients treated with this drug. In fact, dronedarone is contraindicated in patients with a history of heart failure, left ventricular systolic dysfunction, permanent AF, liver and lung toxicity related to previous use of amiodarone, severe renal or hepatic impairment, heart rate <50 b.p.m., second- or third- degree atrio-ventricular block, as well as in subjects taking potent cytochrome P 450 (CYP) 3A4 inhibitors, drugs that induce torsades de pointes or dabigatran [6]. Moreover, post marketing experience has shown that although dronedarone effectively reduces the risk of recurrence of atrial flutter, and in case of recurrence dronedarone slows atrial flutter, in rare cases it may cause an insufficient AV node conduction, leading to 1:1 atrio-ventricular nodal conduction [7]. All of these issues have led to an underuse of dronedarone in clinical practice.

Although patients included in ATHENA and AFFIRM trials are different, we compared the results of both studies after 2 years of follow-up (21±5 months in ATHENA and 24 months in AFFIRM). Compared with patients included in AFFIRM trial, patients included in ATHENA were older, more frequently women, and had more commonly hypertension, valvular disease, and ischemic heart disease. Despite higher risk for cardiovascular outcomes, overall mortality was similar in the placebo group of ATHENA and in the rate-control group of AFFIRM. However, overall mortality was higher in the rhythm-control group of AFFIRM

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Table 1: Clinical Characteristics and Overall Mortality in ATHENA and AFFIRM Trials

Variable	Dronedarone group (AHENA) (n=2301)	Rhythm-control group (AFFIRM) (n=2033)	P	Placebo group (ATHENA) (n=2327)	Rate-control group (AFFIRM) (n=2027)	P
Mean age (years)	71.6±8.9	69.7±9.0	0.0001	71.7±9.0	69.8±8.9	0.0001
Female gender (%)	49.2	37.9	0.0001	44.6	40.6	0.008
Hypertension (%)	86.9	50.1	0.0001	85.8	51.6	0.0001
Ischemic heart disease (%)	29.0	27.6	NS	31.7	24.5	0.0001
Valvular disease (%)	16.5	4.9	0.0001	16.3	4.8	0.0001
Nonischemic cardiomyopathy (%)	5.3	4.7	NS	5.6	4.9	NS
Overall mortality (%)	5	9	0,0001	6	7	NS

compared with the dronedarone group of ATHENA (Table **1**).

In the light of these data, it seems that in selected patients, such as those with paroxysmal or persistent AF without heart failure, a dronedarone based rhythm-control strategy could be the best option of treatment.

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