British Journal of Medicine & Medical Research
5(9): 1088-1095, 2015, Article no.BJMMR.2015.122
ISSN: 2231-0614

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Real-World Observations with Dronedarone Compared to Other Anti-Arrhythmic Drugs in Recurrent Atrial Fibrillation

D. Demarie[1], F. Orlando[1], M. Imazio[1], E. Cerrato[1], E. Richiardi[2*] and R. Belli[1]

[1]Maria Vittoria Hospital, Turin, Italy.
[2]Gradenigo Hospital, Turin, Italy.

Authors' contributions

This work was carried out in collaboration between all authors. Author DD designed the study, wrote the protocol, and wrote the first draft of the manuscript. Author FO managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/12626
Editor(s):
(1) Gaetano Santulli, College of Physicians & Surgeons Columbia University Medical Center New York, NY, USA.
(2) Francesco Angelico, Department of Public Health and Infectious Diseases, Sapienza University Medical School, Rome, Italy.
Reviewers:
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(3) Sam Said, Clinical cardiologist, Hospital Group Twente, The Netherlands.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=716&id=12&aid=6700

Original Research Article

Received 10th July 2014
Accepted 10th October 2014
Published 29th October 2014

ABSTRACT

Background: Many clinical trials have shown that dronedarone which is a potent ion channels blocker is effective in the prevention of atrial fibrillation (AF) relapses.
Objective: The aim of this report is to evaluate the recurrence of AF and safety during therapy with dronedarone.
Methods: From September 2010 to February 2013, 95 patients with recurrent AF were followed by our department. The mean age was 71. Fifty-two were male (55%). All patients were in class NHYA I-II with paroxysmal or persistent AF. Hepatic enzymes were controlled after 1, 3, and 6 months of therapy.
Results: Structural heart diseases were present in 90.5% of patients; 9.5% of patients had lone AF. We observed recurrences of AF in 37.9% of patients treated with dronedarone compared with 39% of patients treated with propafenone or flecainide, 35% of patients treated with sotalol and 25% of patients treated with amiodarone. Using log-rank Mantel-Cox test there are no statistical

**Corresponding author: Email: daniela.demarie@aslto2.piemonte.it;*

significant differences between dronedarone and IC anti-arrhythmic drugs and sotalol (p 0.743; p 0.868).
Conclusion: According to guidelines, dronedarone resulted as effective as other anti-arrhythmic drugs (except amiodarone) in the prevention of AF with the advantage that it may be safely used in a greater number of patients (including elderly patients with structural heart diseases).

Keywords: Atrial fibrillation; recurrent atrial fibrillation; anti-arrhythmic drugs; ion channel blockers.

1. INTRODUCTION

Prevalence and incidence of atrial fibrillation are increasing worldwide; both of them increase with age and with underlying heart disease [1]; in ATRIA study the prevalence of AF was 5.5 percent (ranging from 0.7 percent in those aged 55 to 59 years and 17.8 percent for those ≥ 85 years of age) and it was higher in men than women (6.0 versus 5.1 percent) [2].

Stroke and other thrombo-embolic events, heart failure and hospitalizations, degraded quality of life, reduced exercise capacity, and left doubled by AF, independently of other known predictors of mortality [3].

Therapeutic strategies to prevent atrial fibrillation recurrences include the use of several anti-arrhythmic drugs.

Similarly to amiodarone, dronedarone is a potent blocker of multiple intra-cardiac ion channels (Fig. 1) [4]; its safety and efficacy have been established in many randomized placebo-controlled trials, conducted mostly in patients with history of atrial fibrillation (AF) or atrial flutter and utilizing a variety of primary endpoints including rates of successful maintenance of sinus rhythm following cardioversion, hospitalizations for cardiac causes and death.

Dronedarone was shown in two large pivotal trials to be superior to placebo in maintaining sinus rhythm in patients with recurrent AF [5]. Dronedarone resulted to be generally well tolerated [6]. The safety profile of dronedarone is advantageous in patients without structural heart disease and in stable patients with heart disease. Specifically, dronedarone appears to have a low potential for pro-arrhythmias [5,7]. In the ATHENA trial, in patients who had paroxysmal or persistent AF, dronedarone was associated with a significant reduction in cardiovascular outcome events, including the composite of unplanned cardiovascular hospitalizations and all-cause mortality; other analyses demonstrated a significant reduction in arrhythmic mortality, cardiovascular mortality (including arrhythmic mortality), and stroke [7].

Here we present our experience in a group of patients with history of recurrent atrial fibrillation treated with dronedarone.

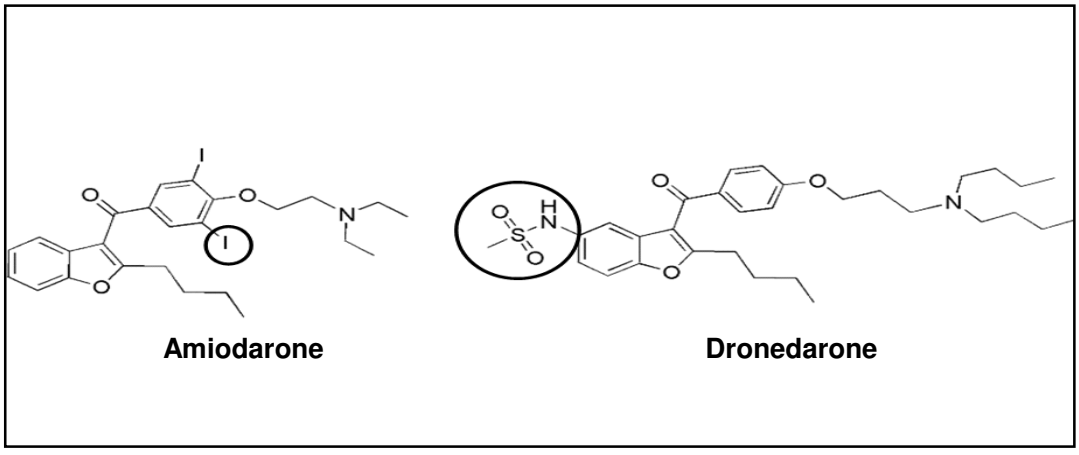

Fig. 1. Chemical structure: dronedarone is a benzofuran derivate; compared with amiodarone, the iodine moieties are not present and a methylsulfonamide group is added to reduce solubility in fats (lipophilicity)

2. MATERIALS AND METHODS

From September 2011 to February 2014, 95 patients who had started treatment with dronedarone for a history of recurrent atrial fibrillation were followed by the departments of Cardiology of two Turin hospitals. The males were 52, the females were 43; the mean age was 71 years (range 44-92 years) (Fig. 2). At the moment of recruitment all the patients were in sinus rhythm and in NYHA class I or II; patients with EF < 40% were excluded. Transaminases were performed 1, 3 and 6 months after the recruitment and if they were altered the treatment was stopped. During the follow up patients were periodically re-evaluated to verify the eligibility to treatment.

An electrocardiogram was repeated every 3 months or when the patients reported symptoms that were compatible with arrhythmias.

The primary end-point was the first recurrence of AF.

3. STATISTICAL ANALYSIS

Continuous variables were expressed as mean ± standard deviation or median (first-third quartile) and compared by Student's unpaired t-test. Categorical variables were expressed as counts and percentages and compared by the Chi-square test or Fisher's exact test as appropriate. The statistical differences between the groups were assessed using Kaplan-Meier analysis, log-rank test and Cox proportional hazard model estimating freedom from atrial fibrillation. Computations were performed with SPSS 20 (IBM, Armonk, NY, USA).

4. RESULTS

Structural heart diseases were present in 86 patients (90, 5%); they consisted in:

- hypertension in 78 patients (82.1%)
- previous PTCA in 42 patients (44.2%)
- valvular disease in 4 patients (4.2%)

Nine patients (9.5%) had no structural heart disease (lone atrial fibrillation; Fig. 3).

At the beginning of therapy, 86 patients (90.5%) had a high thromboembolic risk with CHADSVASC score ≥ 2.

The average duration of follow up was 19, 2 months. Dronedarone was stopped prudentially in two cases because of mild increase of hepatic enzymes and in other two cases because of a worsening of renal function. Three (3,1%) patients died during the follow-up: one died suddenly after 3 months of therapy (the information was given by his relatives and no more details are available), the other two patients died for non cardiac causes (one of them was 90 years old).

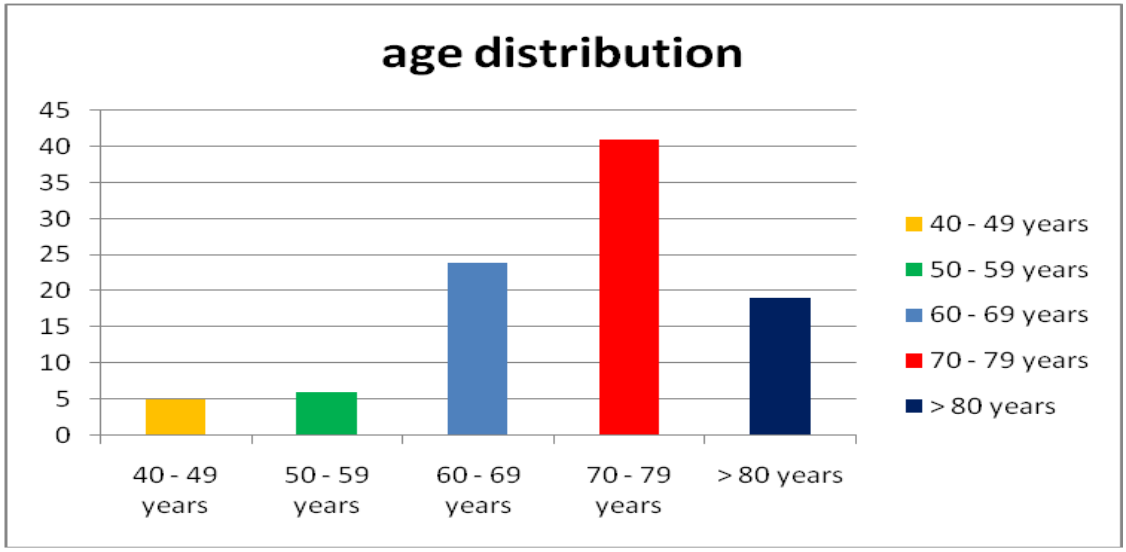

Fig. 2. Age distribution: The vast majority of our patients are in the seventh decade

Thirty-six patients experienced recurrences of atrial fibrillation (37.9%). Three of them were then treated with ablation.

There were no cases of heart failure, respiratory insufficiency, increase of QT interval or thyroid dysfunction.

At the end we compared the results in the dronedarone group with 181 patients who were evaluated in the same period for recurrent atrial fibrillation and who were treated with different anti-arrhythmic drugs.

We found recurrences of atrial fibrillation in the 39% of the 71 patients treated with propafenone (600-900 mg die) or flecainide (100-200 mg die), in the 35% of the 64 patients treated with sotalol (80-160 mg die) and in the 25% of the 46 patients treated with amiodarone (200 mg die).

Using log-rank Mantel-Cox test we could not find any statistical significant difference neither between dronedarone and IC anti-arrhythmic drugs ($p= 0.743$) nor between dronedarone and sotalol ($p= 0.868$).

Only in the comparison between dronedarone and amiodarone there is a clear trend in favor of amiodarone in terms of reduction of recurrences of AF ($p= 0.139$) (Fig. 4 a-b).

5. DISCUSSION

In AF the use of anti-arrhythmic drugs is limited by potentially serious side effects (including pro-arrhythmic effects and pulmonary toxicity) which may lead to a reduced clinical efficacy of rhythm control strategies; at present randomized trials found rate control to be not inferior to rhythm control for the prevention of cardiovascular mortality and morbidity [8,9,10].

Because of side effects of anti-arrhythmic drugs, the recent guidelines for the management of AF consider the rhythm control strategy clearly better than the rate control only when it is necessary to improve symptoms [11,12].

The impact of miRNAs in electrical and structural remodeling of the cardiac tissue, as it has been shown by recent studies, points to potential novel mechanism-based therapeutic targets [13].

Until new drugs become available, what clinicians may do is to choose among traditional anti-arrhythmic drugs the ones which offer each patient the best risk-benefit ratio.

Dronedarone is an amiodarone analogue from which it differs structurally in that the iodine moiety has been removed and a methane-sulfonyl group has been added.

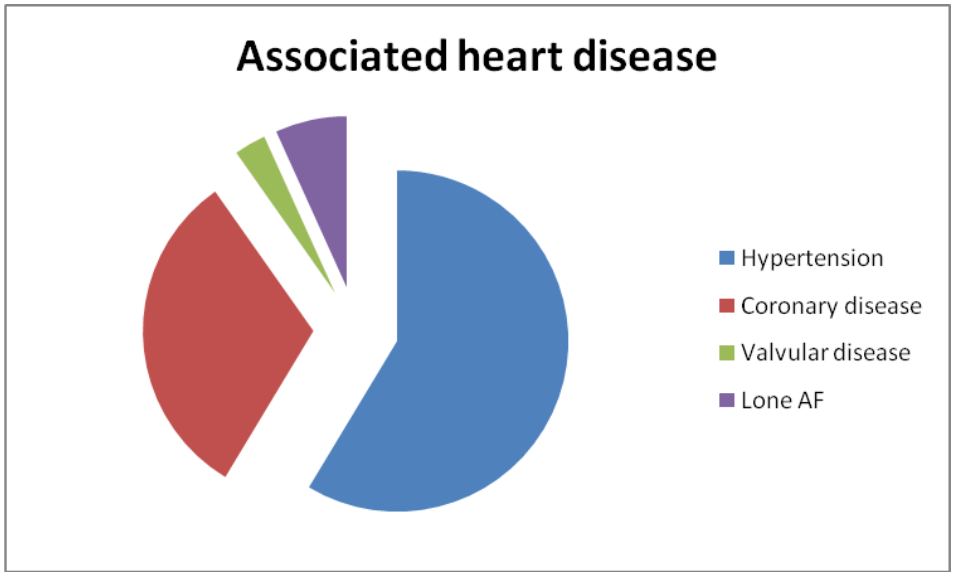

Fig. 3. Associated heart diseases: history of hypertension was present in 78 patients (82.1%), previous PTCA in 42 patients (44,2%), valvular heart disease in 4 patients (4,2%); lone atrial fibrillation was present in 9,5% of the patients

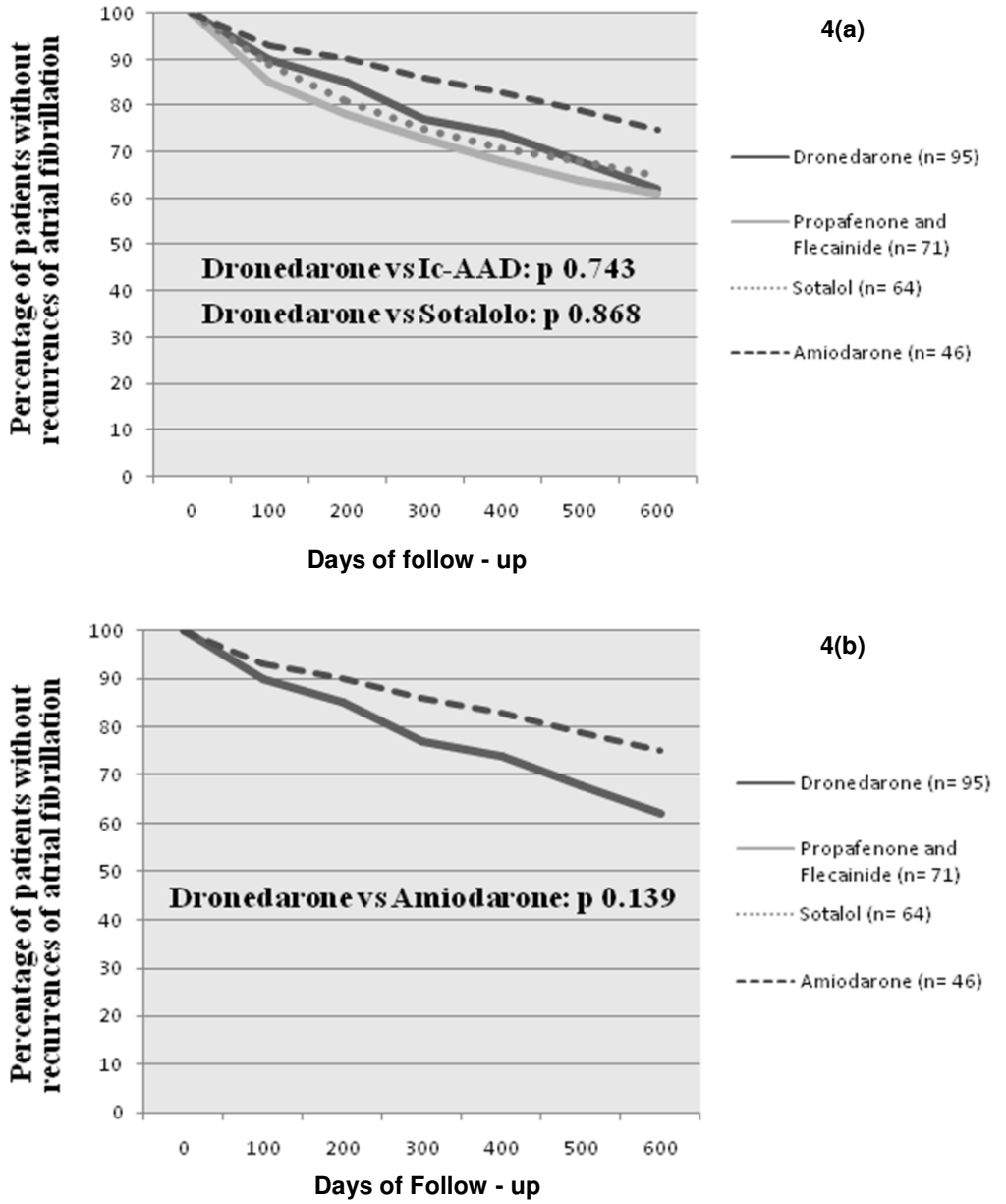

Fig. 4 a-b. Comparison between dronedarone and other AAD in terms of percentage of patients without recurrences of Atrial Fibrillation: 4a) there is no significant difference neither in the comparison between dronedarone and IC anti-arrhythmic drugs (p 0.743) nor between dronedarone and sotalol (p 0.868); 4b) in the comparison between dronedarone and amiodarone there is a clear trend in favor of amiodarone (p 0.139)

These modifications reduce thyroid and other organ adverse effects and make dronedarone less lipophilic, shortening its half-life [4].

In Athena trial dronedarone compared with placebo reduced the incidence of hospitalization due to cardiovascular events or death in patients with AF; so Dronedarone is the only anti-arrhythmic drug that has shown a beneficial effect on mortality; this is a first evidence that maintaining sinus rhythm may prevent relevant outcomes in AF [7]. According to a post hoc analysis from EURIDIS, ADONIS, and ATHENA trials, patients with lone AF had a high risk for

cardiovascular hospitalization within 1 year. Dronedarone reduced the risk of cardiovascular hospitalizations in this population when added to standard of care [14].

Coronary heart disease is prevalent among AF patients and limits anti-arrhythmic drug use because of their potentially life-threatening ventricular pro-arrhythmic effects.

In a recent *post hoc* analysis [15], dronedarone on top of standard care in AF patients with CHD reduced cardiovascular hospitalization or death similar to that in the overall ATHENA population, and reduced the occurrence of first acute coronary syndromes. Importantly, the safety profile in this subpopulation was also similar to that of the overall ATHENA population, with no excess in pro-arrhythmias.

Since no pro-arrhythmia has been documented with its use, dronedarone may be safely used in patients with left ventricular hypertrophy, where the risk from anti-arrhythmic drugs is thought to be related to torsades de pointes.

For patients in NYHA functional class III or IV, there is evidence from the ANDROMEDA trial that these patients may derive harm from dronedarone therapy [16].

Freemantle N. et al. performed an analysis of electronic databases of 39 randomized controlled trials examining amiodarone, dronedarone, flecainide, propafenone, sotalol, or placebo for the treatment of AF. Amiodarone has been demonstrated to be the most effective drug in maintaining sinus rhythm and differences in outcomes between the anti-arrhythmic drugs were reported: sotalol and possibly amiodarone increased mortality, while dronedarone decreased the incidence of serious adverse events and pro-arrhythmia [17].

According to the recent guidelines, dronedarone is a first choice anti-arrhythmic drug in all subsets of patients but the ones with heart failure; sotalol is a first line drug only in patients with coronary heart disease besides the ones with minimal or absent heart disease; flecainide and propafenone may be used only in the absence of significant heart disease. Due to its potential side effects and despite its greater anti-arrhytmic efficacy, amiodarone is a second line drug in all patients excepting the ones with heart failure [12].

In our observational study in patients with a history of recurrent AF, we compared the benefit/risk ratio of dronedarone with other anti-arrhythmic drugs when each drug was administered according to guidelines indications.

As in Athena study [7], patients treated with dronedarone were older (the vast majority of them ≥70 years old), mostly with structural heart disease (9 patients with lone AF compared with 86 patients with hypertension, CAD or valvular heart disease) and with $CHADS_2VA_2Sc$ score ≥ 2. None had acute heart failure; in fact we used the drug only in NYHA I or NYHA II class patients. We did not use the drug in permanent AF [18] and in case of severe renal failure (creatinine clearance < 30 ml/min).

Dronedarone resulted well tolerated; we did not observe pulmonary or liver toxicity; in two patients the drug was stopped prudentially because of a mild increase of hepatic enzymes and in other two cases because renal function worsening (in all these cases hepatic and renal functions were completely restored after the discontinuation of the drug). Only one patient died at follow up for probable cardiac causes: he was a patient with CAD and normal ejection fraction in which dronedarone had been started for persistent AF after failure of other anti-arrhythmic drugs.

After an average follow up of 19.2 months the efficacy of dronedarone in preventing recurrences of AF was clearly lower than amiodarone (albeit not reaching a statistical significance, probably due to the small sample) but comparable with other anti-arrhythmic drugs.
In conclusion, in our small series of patients with paroxysmal or persistent AF, according to guidelines indications, dronedarone resulted as efficacious as other anti-arrhythmic drugs (but amiodarone) with the advantage due to its less toxicity that it may be safely used in a larger number of patients (including elderly with structural cardiac disorders). The main limitations of our observational study consist in the small sample (probably responsible for not reaching a statistical significance in the comparison of dronedarone with amiodarone) and in the non-comparability of groups treated with different anti-arrhythmic drugs (even if non-comparability was accepted from the beginning willing to administer each drug only to the specific subgroup of patients suggested by the guidelines).

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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