**Effects of Dronedarone on Clinical Outcomes in Patients with Lone Atrial Fibrillation:** Pooled Post Hoc Analysis from the ATHENA/EURIDIS/ADONIS Studies

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Dronedarone in Lone Atrial Fibrillation. **Introduction:** Dronedarone has been shown to reduce cardiovascular hospitalizations or death in patients with atrial fibrillation (AF) and additional risk factors. This post hoc exploratory analysis examines its effects in the subgroup of lone AF patients.

**Methods and Results:** Individual data from patients with lone AF enrolled in the EURIDIS, ADONIS, and ATHENA trials were entered in a central database. The effects of dronedarone compared to placebo on the composite endpoint of cardiovascular hospitalizations or death, and their individual components, were evaluated. A total of 432 (192 placebo and 240 dronedarone) patients (7% of the total population) were classified as having lone AF (69.4% male patients, mean age 64 ± 13 years). The patients were followed for 13.8 ± 7.2 months. The risk for first cardiovascular hospitalizations or death from any cause in the placebo group after 1 year was 25% in the lone AF group compared to 29% the rest of the population. For patients with lone AF, dronedarone led to a 44% reduction of cardiovascular hospitalizations or death (hazard ratio [HR] 0.56; 95%CI 0.36–0.88, P = 0.004) and to a 46% reduction in cardiovascular hospitalizations alone (HR 0.54; 95%CI 0.34–0.87, P = 0.004) compared to placebo. HR for all-cause mortality was 1.02 (95%CI 0.31–3.34, P = 0.885). All findings were homogeneous across the 3 studies and similar to those observed in the overall population.

**Conclusion:** According to this post hoc analysis, patients with lone AF have a high risk for cardiovascular hospitalization within 1 year. Dronedarone when added to standard of care reduces the risk of cardiovascular hospitalizations in this population. (J Cardiovasc Electrophysiol, Vol. pp. 1-7

antiarrhythmic therapy, cardiovascular hospitalization, dronedarone, lone atrial fibrillation

**Introduction**

Atrial fibrillation (AF) is the most commonly encountered cardiac rhythm disturbance. In the United States, hospitalizations for AF have increased 2- to 3-fold in recent years1 demonstrating the enormous economic burden of this arrhythmia. The most significant consequences of AF include congestive heart failure, a 5-fold increase in the risk of stroke, and a 2-fold increase in mortality.2 The majority of the patients have cardiovascular comorbidities and other risk factors for hospitalization. There is, however, a subset of patients who have AF in the absence of structural heart disease and of extracardiac disorders. This condition is termed lone AF.3 In younger patients with lone AF, catheter ablation therapy has evolved as an established therapeutic approach.4 However, ablation therapy is difficult to perform, not widely available, and the rate of major complications is still significant.5 Therefore, pharmacological therapy remains an option even in these patients. Currently available antiarrhythmic drugs have limited efficacy in preventing AF recurrences, not all of them have rate-controlling properties in case of relapsing AF, and some are known to have unfavorable safety profiles. Dronedarone is a new multichannel blocking drug that has been demonstrated in the EURopean trial In AF or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm (EURIDIS) and the American–Australian–African trial with DronedarONe In AF or flutter patients for the maintenance of Sinus rhythm (ADONIS) trials to be more effective than placebo in maintaining normal sinus rhythm and in controlling the ventricular rate during AF recurrences but with a comparable side effect profile to placebo.6 Moreover, in the 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) trial, dronedarone has been shown to reduce important clinical endpoints such as cardiovascular hospitalizations or death in patients with AF and additional risk factors.

There is a paucity of data regarding the prevalence of lone AF in large samples of AF patients and with respect to the associated incidence of major clinical events. Thus, the purpose of the present study was to establish the incidence of clinical events in patients with lone AF and to evaluate the effects of dronedarone on clinical outcomes in this selected patient population.

**Methods**

**Patient Population and Procedures**

Individual data from patients with lone AF enrolled in the EURIDIS, ADONIS, and ATHENA trials were entered in a central database. The institutional review board at each site approved the study, and all patients gave written informed consent for taking part in the studies. In brief, all 3 studies enrolled patients with paroxysmal or persistent AF. In EURIDIS and ADONIS, patients had to be in sinus rhythm for at least 1 hour before randomization whereas in ATHENA, patients could be either in sinus rhythm or in AF at randomization. Patients with permanent AF or with unstable hemodynamic conditions were excluded from participation in any of the three studies. Lone AF was defined as AF occurring in patients without structural heart disease or arterial hypertension, and without extracardiac diseases associated with AF (i.e., thyroid disorders). Due to missing baseline data, 20 patients (2 in EURIDIS, 5 in ADONIS and 13 in ATHENA) could not be classified as to the presence or absence of lone AF. These patients were not included in the present analysis. In all 3 studies, 8 patients were randomly assigned to double-blind treatment with dronedarone 400 mg BID or matching placebo. Hospitalization was defined as at least 1 overnight stay. The main outcome measure of this posthoc analysis was the time to the composite endpoint of first hospitalization for cardiovascular reasons or death from any cause; secondary outcome measures were time to first hospitalization for cardiovascular reasons and time to death from any cause. The EURIDIS, ADONIS, and ATHENA studies were sponsored by Sanofi-Aventis.

**Statistical Methods**

Baseline parameters of patients with and without lone AF were compared with logistic regression analysis for qualitative and an ANOVA test for quantitative variables. Cumulative incidence curves were estimated utilizing the Kaplan–Meier method and compared by the log-rank test. The hazard ratios and 95% confidence intervals of the composite endpoint and its individual components were calculated by means of a Cox model adjusted on studies separately in patients with and without lone AF. The absolute risk reduction (ARR) and the number needed to treat (NNT) were computed from the hazard ratios and the survival rates at 1 and 2 years in the placebo group where a survival difference between the two groups was present. All P-values are two-tailed, and statistical significance was assumed at a P-value of 0.05 or smaller.

**Results**

**Patient Population**

The 3 randomized clinical trials comprised a total of 5,845 AF patients. Of those, 432 patients (192 on placebo, 240 on dronedarone) met the definition lone AF (frequency 7%). Baseline clinical characteristics are depicted in Table 1. Compared to the remaining patients, patients with lone AF were younger, more likely male, had lower blood pressure, and received less cardiovascular medications. The average study follow-up time of patients with lone AF was 13.8 ± 7.2 months.

**Composite Outcome of Time to First Cardiovascular Hospitalization or Death**

Among lone AF patients assigned to receive placebo medication, the risk for cardiovascular hospitalization or death was 25% (95% CI, 18–32%) at 1 year. This risk was similar to that of the remaining patient population (29% at 1 year; 95% CI, 27–31%) (Table 2). Dronedarone therapy was associated with a hazard ratio (HR) of 0.56 (95% CI 0.36–0.88, \( P = 0.004 \), Fig. 1) for the primary outcome measure. The NNT to prevent 1 endpoint event in the lone AF population was 10 (95% CI: 7; 37, ARR 0.10, 95% CI 0.03; 0.15) at 1 year compared with 17 (95% CI: 13; 26, ARR 0.06, 95% CI 0.04; 0.08) in patients with other type of AF. An additional analysis was performed adding the following possible prognostic factors as covariates in the Cox regression model: age, gender, baseline medication (beta blocker, anticoagulants, and antiplatelet drugs). This analysis gave similar results (HR = 0.59; 95%CI 0.38–0.93). The effect of dronedarone

### Table 1

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of Baseline Characteristics in Patients with or without Lone AF</th>
<th>Patients with Lone AF</th>
<th>Patients without Lone AF</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>( N = 432 )</td>
<td>( N = 5,413 )</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Age, years (SD)</td>
<td>63.5 (13.3)</td>
<td>70.3 (9.6)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>300 (69.4)</td>
<td>3,005 (55.5)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Structural heart disease, n (%)</td>
<td>0 (0.0)</td>
<td>3,239 (60.3)</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>0 (0.0)</td>
<td>4,697 (86.8)</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg (mean (SD))</td>
<td>127.0 (14.7)</td>
<td>134.3 (17.7)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg (mean (SD))</td>
<td>76.3 (9.0)</td>
<td>78.2 (10.5)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>CAD, n (%)</td>
<td>0 (0.0)</td>
<td>1,659 (30.6)</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>CHF, n (%)</td>
<td>0 (0.0)</td>
<td>1,580 (29.2)</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>Medication at baseline, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blocking agents</td>
<td>155 (35.9)</td>
<td>3,666 (67.7)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors or ARBs</td>
<td>0 (0.0)</td>
<td>3,748 (69.2)</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>221 (51.2)</td>
<td>3,339 (61.7)</td>
<td>0.907</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>0 (0.0)</td>
<td>2,802 (51.8)</td>
<td>NC</td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>65 (15.0)</td>
<td>2,040 (37.7)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Chronic antiplatelet therapy</td>
<td>141 (32.6)</td>
<td>2,416 (44.6)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>Calcium antagonists with heart rate lowering effects</td>
<td>43 (10.0)</td>
<td>749 (13.8)</td>
<td>0.055</td>
<td></td>
</tr>
<tr>
<td>Digitalis</td>
<td>66 (15.3)</td>
<td>782 (14.4)</td>
<td>0.616</td>
<td></td>
</tr>
</tbody>
</table>

CHF: chronic heart failure; CAD: coronary artery disease; ACE: angiotensin converting enzyme, ARB: angiotensin II receptor antagonist; NC: nonconvergence of the logistic regression.

P-value comparing the lone AF population to the nonlone AF population using a logistic regression for qualitative variables and an ANOVA for quantitative variables, both adjusted on study.
TABLE 2
Unadjusted Analysis of Time from Randomization to First Cardiovascular Hospitalization or Death from Any Cause

<table>
<thead>
<tr>
<th>Endpoint’s composition</th>
<th>Number of Patients with Endpoint</th>
<th>Hazard ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV hospitalization</td>
<td>42 (N = 192)</td>
<td>0.562 [0.361;0.877]</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>4 (N = 192)</td>
<td>0.771 [0.701;0.847]</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>2 (N = 192)</td>
<td></td>
</tr>
<tr>
<td>Non cardiovascular death</td>
<td>2 (N = 192)</td>
<td></td>
</tr>
</tbody>
</table>

CV: cardiovascular.
* Determined from the cause-specific Cox regression model adjusted on studies.
† Hazard ratio from the Cox model is adjusted on studies. P-value of interaction = 0.08.

on the combined endpoint (Table 2) was comparable in lone AF patients and in patients not classified as lone AF. The effect was homogeneous across the three studies contributing to the present analysis (Table 3).

**Cardiovascular Hospitalization**

With respect to cardiovascular hospitalizations alone, in patients with lone AF the HR was 0.54 (95% CI 0.34–0.87, P = 0.004) (Table 4). The effect of dronedarone on cardiovascular hospitalizations alone (Table 4, Figs. 2 and 3) was comparable in lone AF patients and in patients not classified as having lone AF at baseline. The NNT to prevent a CV hospitalization in the first year in patients with lone AF was 10 (95% CI: 7; 37, ARR 0.10, 95% CI: 0.03; 0.15) compared with 17 (95% CI: 13; 25, ARR 0.06, 95% CI: 0.04; 0.08) in the patients with other types of AF. Adjusted analysis adding the aforementioned prognostic factors in the model gave similar results (HR = 0.57; 0.36–0.92). The majority of cardiovascular hospitalizations represented hospitalizations for treatment of AF or other supraventricular arrhythmias. In the placebo group 30 of 42 (71%) cardiovascular hospitalizations were for AF or other supraventricular arrhythmias compared to 16 of 30 (53%) in the dronedarone group.

**Mortality**

There were no significant differences in all-cause mortality (HR: 1.02; 95% CI 0.31–3.34, P = 0.885) and in cardiovascular mortality (HR: 1.27; 95% CI 0.21–7.63, P = 0.879) in lone AF patients assigned to dronedarone or placebo. All the above findings were similar to those observed in patients not classified as lone AF (Fig. 3).

**Adverse Events**

Figure 4 depicts the side effect profile of dronedarone compared to placebo for patients with lone AF and other types of AF. There was no significant interaction between the adverse events and type of AF. Specifically, adverse events occurred in 126 of 192 placebo patients (65.6%) and 164 of 240 dronedarone patients (68.3%) with lone AF, and 1,726 of 2,518 placebo patients (68.6%) and 2,040 of 2,874 dronedarone patients (71.0%) with other types of AF. As...
The present analysis comprises the largest series of lone AF patients published to date. The frequency of lone AF in the ATHENA, EURIDIS, and ADONIS studies was 7%. Patients with lone AF assigned to receive placebo medication have a 25% risk to be hospitalized for cardiovascular reasons or to die within 1 year, compared with a 29% risk in patients who were classified not having lone AF. Dronedarone when added to standard of care including rate control medication leads to a 44% reduction of the risk of cardiovascular hospitalizations or death in patients with lone AF (compared with a 23% reduction in those classified without lone AF). Thus, the beneficial effect of dronedarone on clinical events is as significant in patients with lone AF as it is in patients with cardiovascular comorbidities.

Discussion

Main Findings

The prevalent of lone AF was first described in 1954 with a reported prevalence of this arrhythmia between from 2% and 30%. The 7% frequency observed in this analysis, which is based on data from 3 large randomized clinical trials of dronedarone in AF patients, fits well within this range. Obviously, the inclusion criteria of the 3 trials are a major determinant of this frequency. For instance, the largest of these studies (ATHENA) requested an age of ≥70 years to be eligible for participation. The likelihood of lone AF, however, is highest in younger patients. Thus, the 7% frequency of lone AF almost certainly is an underestimation of the true prevalence across all age groups.

Prevalence of Lone AF

In several previous reports, lone AF seemed to be a benign arrhythmia. For instance, Jahangir et al. followed 76 patients with lone AF (age at diagnosis 44 ± 12 years) for over 3 decades and found similar rates of survival, of freedom from congestive heart failure or stroke as in patients without AF. There was a 29% cumulative probability of progression to permanent AF over 30 years follow-up. The only predictor for these endpoints was the age at the time of diagnosis of AF. A 30-year follow-up of 276 lone AF patients in the Framingham study indicated similar rates of coronary heart disease and congestive heart failure as in patients with sinus rhythm, but the rate of strokes was significantly greater in the lone AF group. Other investigators described additional factors influencing the prognosis of lone AF patients such as the permanent form of AF or left atrial volume.

Prognostic Implications of Lone AF

As recently suggested by Pinter and Dorian, the primary aim of therapy of AF should be the treatment of the patient and not of the ECG. It is thus important to note that only limited experience is available about the risk of hospitalization for cardiovascular reasons in patients with lone AF. In a study investigating the pill-in-the-pocket strategy, hospitalization rate was lower after initiation of the therapy than the year before. However, there are some important differences between this study and ours. First, half of the patients in the previous study had structural heart disease and/or arterial hypertension. This was not the case

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Figure 3. Hazard ratios (dronedarone 400 mg BID vs placebo) and 95% confidence intervals of primary and secondary endpoints according to lone AF. 
\(a\): Determined from the Cox regression model, adjusted on studies; \(b\): \(P\)-value of interaction between baseline lone AF and treatment based on the Cox regression model, adjusted on studies.

Figure 4. Hazard ratios (dronedarone 400 mg BID vs placebo) and 95% confidence intervals of adverse events in patients exposed to study drug according to lone AF. 
\(a\): Determined from the Cox regression model, adjusted on studies. \(b\): \(P\)-value of interaction between baseline lone AF and treatment based on the Cox regression model, adjusted on studies.

in our study. Second, Alboni et al. tested the efficacy of medication in all patients during an in hospital stay and thereby selected a “responder population.” Our analysis was not done in a selected responder population; instead, all patients with lone AF enrolled in the 3 pivotal studies on dronedarone were considered. Recently, the clinical importance of hospitalization has been emphasized in numerous reports. For instance, a recent report from the EuroHeart Survey showed that approximately a third of all AF patients had to be hospitalized within 1 year of follow-up, indicating the magnitude of this outcome measure.\(^{15}\) Such hospitalizations impact in a very negative way with the perceived quality of life of patients with AF.\(^{16}\) Perhaps even more importantly, a post hoc analysis of the AFFIRM trial demonstrated that cardiovascular hospitalizations were very predictive of subsequent mortality that was basically doubled compared to patients without the need for hospital admission.\(^{17}\) The present analysis expands our knowledge concerning these issues by demonstrating that even in patients with lone AF there is a substantial risk of cardiovascular hospitalization. In fact, the risk was not significantly different from that observed in patients with AF in the setting of structural heart disease.

Effects of Dronedarone in Lone AF

According to current guidelines,\(^2\) AF patients without heart disease can receive antiarrhythmic drug therapy with flecainide, propafenone or sotalol as first line therapy, followed by amiodarone. Catheter ablation can be considered after failure of at least 1 antiarrhythmic drug. All of these compounds, however, carry a distinct risk of extracardiac and/or cardiac side effects, notably proarrhythmic risk.\(^{18}\) Moreover, for none of these compounds have been beneficial effects demonstrated on important clinical endpoints.
Dronedarone on the other hand has been demonstrated to substantially reduce the risk for cardiovascular hospitalization or mortality in patients with paroxysmal or persistent AF. Although the compound is less effective than its mother compound amiodarone in maintaining sinus rhythm, the incidence of important clinical outcomes was significantly reduced by the drug. The present analysis, which was derived from 3 pivotal randomized dronedarone trials, extends these observations to the group of elderly patients with lone AF. In these patients, there was a significant reduction in the risk of the composite endpoint of cardiovascular hospitalization or death. This endpoint was clearly driven by less frequent hospital admissions for the treatment of AF. In this relatively healthy subgroup of patients the number of deaths was too small to access clinically meaningful differences in mortality between dronedarone and placebo-treated patients. Similar to the entire trial patient population, dronedarone was extremely well tolerated in lone AF patients. Thus, this novel antiarrhythmic drug seems to represent an attractive alternative to commonly used antiarrhythmic drugs such as the class IC compounds in this patient cohort. Such a recommendation has recently been expressed in the new European guidelines for the management of AF.

Limitation of the Study

Although the most frequent cause for cardiovascular hospitalization was AF or other supraventricular arrhythmias, no systematic data were available about maintenance of sinus rhythm or on the impact of the therapy on symptoms not leading to hospitalization, especially as the largest of the analyzed studies (ATHENA) did not collect systematic data on these issues.

Conclusions

Based on this post hoc analysis of 3 major randomized trials of dronedarone in patients with paroxysmal or persistent AF, elderly patients with lone AF face a high likelihood of cardiovascular hospitalization. They derive similar benefit regarding a reduction in cardiovascular hospitalization from treatment with dronedarone than patients with AF in the setting of structural heart disease.

References

