Efficacy and safety of dronedarone across age and sex subgroups: a post hoc analysis of the ATHENA study among patients with non-permanent atrial fibrillation/flutter

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Aims
Age and sex may impact the efficacy of antiarrhythmic drugs on cardiovascular outcomes and arrhythmia recurrences in patients with atrial fibrillation (AF). We report on a post hoc analysis of the ATHENA study (NCT00174785), which examined cardiovascular outcomes in patients with non-permanent AF treated with dronedarone vs. placebo.

Methods and results
Efficacy and safety of dronedarone were assessed in patients according to age and sex. Baseline characteristics were comparable across subgroups, except for cardiovascular comorbidities, which were more frequent with increasing age. Dronedarone significantly reduced the risk of cardiovascular hospitalization or death due to any cause among patients 65–74 [n = 1830; hazard ratio (HR) 0.71, 95% confidence interval (CI) 0.60–0.83; P < 0.0001] and >75 (n = 1925; HR 0.75, 95% CI 0.65–0.88; P = 0.0002) years old and among males (n = 2459; HR 0.74, 95% CI 0.64–0.84; P < 0.00001) and females (n = 2169; HR 0.77, 95% CI 0.67–0.89; P = 0.0002); outcomes were similar for time to AF/AFL recurrence. Among patients aged <65 years (n = 873), cardiovascular hospitalization or death due to any cause with dronedarone vs. placebo was associated with an HR of 0.89 (95% CI 0.71–1.11; P = 0.3). The incidence of all treatment-emergent adverse events (TEAEs) and TEAEs leading to treatment discontinuation was comparable among males and females, and increased with increasing age.

Conclusions
These results support the use of dronedarone for the improvement of clinical outcomes among patients aged >65 years and regardless of sex.

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Keywords
Antiarrhythmic drug • Atrial fibrillation • Cardiovascular outcomes • Dronedarone

Introduction

Atrial fibrillation (AF) is a common arrhythmia that is more prevalent with increasing age and is associated with an increased risk of stroke, heart failure, and death. \(^1\) The risk of developing AF is 1.5 times higher in males compared with females; additionally, the prevalence of AF does not change with age in females, while it increases with advancing age in males. \(^3\) However, females with AF are at a greater risk for stroke and death and experience a greater burden of symptoms and a poorer quality of life compared with males. \(^4\)

Anti-arrhythmic drug therapy is a treatment option for the management of AF if a rhythm control strategy is warranted. \(^1\) \(^5\) Dronedarone, an antiarrhythmic drug with characteristics of all four Vaughan-Williams classes, is indicated to reduce the risk of AF-related hospitalizations in patients with a history of paroxysmal/permanent AF who are in sinus rhythm. \(^6\) In ATHENA (‘A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg b.i.d. for the Prevention of Cardiovascular Hospitalization or Death From any Cause in Patients with Atrial Fibrillation/Flutter’; NCT00174785), the largest placebo-controlled trial of an antiarrhythmic drug to date, dronedarone demonstrated a significant reduction in the incidence of the primary composite endpoint of first cardiovascular hospitalization or death due to any cause compared with placebo. \(^7\)

What’s new?
• This post hoc analysis of the ATHENA study in patients with nonpermanent atrial fibrillation/flutter (AF/AFL) assessed clinical outcomes by age and sex subgroups.
• Dronedarone significantly reduced the risk of cardiovascular hospitalization or death and AF/AFL recurrence compared with placebo among patients aged 65–74 years and ≥75 years, and in both males and females.
• The incidence of all treatment-emergent adverse events, including events leading to treatment discontinuation, was comparable among males and females, and increased with increasing age.

Graphical Abstract

Efficacy and safety of dronedarone for atrial fibrillation across age and sex subgroups

In this post hoc analysis of ATHENA among patients with nonpermanent atrial fibrillation/flutter (AF/AFL), dronedarone significantly reduced the risk of first cardiovascular hospitalization or death due to any cause (primary endpoint of ATHENA) compared with placebo:
• Among patients ≥65 years of age and
• Among males and females

No new safety signals were identified across age and sex subgroups
• Incidence of dronedarone treatment-emergent adverse events including those leading to treatment discontinuation:
  – Increased with increasing age (a similar trend was also noted among placebo-treated patients)
  – Was comparable among males and females
• QTc interval (Bazett formula) was slightly prolonged with dronedarone, as expected, and was similar across age and sex subgroups

Keywords
Antiarrhythmic drug • Atrial fibrillation • Cardiovascular outcomes • Dronedarone
Methods

Overview of the ATHENA study
ATHENA was a double-blind, placebo-controlled randomized study that evaluated outcomes among 4628 patients with paroxysmal or persistent AF/AFL. Patients were enrolled between June 2005 and December 2006 and received dronedarone (400 mg twice daily) or a placebo. The study design and primary results have been previously reported. Upon initiation of the study, patients ≥70 years of age or those with at least one pre-specified cardiovascular risk factor were eligible for enrolment. Based on initial results, the eligibility criteria for ATHENA were amended to limit enrolment to patients with higher risk, i.e., patients ≥70 years of age with at least one of the pre-specified cardiovascular risk factors or patients ≥75 years of age. The composite of first cardiovascular hospitalization or death due to any cause was assessed as the primary endpoint. First cardiovascular hospitalization, death due to any cause, and cardiovascular death were assessed as secondary endpoints. The minimum follow-up duration was 12 months.

All patients in the ATHENA study provided written informed consent. The study was approved by independent review boards at participating sites and was conducted according to the Declaration of Helsinki.

Post hoc analysis
The aim of the current post hoc analysis of the ATHENA study was to assess efficacy and safety outcomes of dronedarone vs. placebo by age (<65 years, 65–74 years, and ≥75 years) and sex subgroups. Efficacy outcomes included a composite of first cardiovascular hospitalization or death due to any cause, first cardiovascular hospitalization, death due to any cause, cardiovascular death, and first AF/AFL recurrence (assessed among patients in sinus rhythm at baseline). Baseline demographic and cardiovascular disease-related characteristics and descriptive safety data were summarized.

Statistical analysis
Baseline characteristics and safety data were summarized using descriptive statistics. Efficacy outcomes were assessed in the intent-to-treat patient population, and safety outcomes were assessed in patients who received at least one dose of the study drug. Cumulative incidence functions were calculated using the Kaplan-Meier method. For comparison between treatment groups, hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using a Cox regression model with the treatment group as the only factor. Interaction between age and sex was assessed using a Cox regression model containing treatment group, sex, and age as main effects, and an interaction effect for sex and age. For assessment of QTc interval prolongation, the median of each patient’s values during the course of the study was determined, and the median of the data of all patients in a subgroup was compared with the baseline value. Data were analysed with SAS version 9.4 (Cary, NC, USA).

Results
Of 4628 patients who were randomized to dronedarone (n = 2301) or placebo (n = 2327) in the ATHENA study, 873 (19%), 1830 (40%), and 1925 (42%) were <65 years, 65–74 years, and ≥75 years of age, respectively; 2459 (53%) were males. Median duration of follow-up ranged between 18.6 and 23.9 months in the three age subgroups and between 20.7 (females) and 21.7 (males) months in the sex subgroups. Across age and sex subgroups, the proportion of patients who discontinued treatment during the course of the trial was similar and ranged from 29.0% to 32.6% in both dronedarone and placebo arms (Supplementary material online, Table S1).

Baseline characteristics
Overall, baseline characteristics were comparable in the dronedarone and placebo treatment arms across age and sex subgroups (Table 1). The proportion of males and females was balanced between treatment groups. As expected, CHA2DS2-VASc scores were higher with increasing age and in females compared with males. The prevalence of structural heart disease and coronary heart disease increased with increasing age; males had a higher prevalence of coronary heart disease than females. Concomitant use of medications at baseline was comparable across age and sex subgroups except for slightly lower use of beta-blocking agents and angiotensin-converting enzyme inhibitors/angiotensin II receptor antagonists among patients aged ≥75 years compared with younger patients and slightly lower use of vitamin K antagonists in females vs. males (Supplementary material online, Table S2).

Efficacy
Efficacy outcomes by age and sex subgroups are summarized in Figure 1. Dronedarone vs. placebo significantly reduced the risk of the composite of first cardiovascular hospitalization or death due to any cause (Figure 2), driven by first cardiovascular hospitalization, among patients aged 65–74 (HR 0.71, 95% CI 0.60–0.83; P < 0.0001) and ≥75 (HR 0.75, 95% CI 0.65–0.88; P = 0.0002) years; the risk of first AF/AFL recurrence was also significantly reduced in these two older subgroups (HR 0.76, 95% CI 0.68–0.86; P < 0.0001 and HR 0.72, 95% CI 0.64–0.82; P < 0.0001, respectively). No significant difference was detected in the above outcomes with dronedarone vs. placebo in the smaller group of patients <65 years of age, with HR of 0.89 (95% CI 0.71–1.11; P = 0.3) for first cardiovascular hospitalization or death due to any cause and HR of 0.96 (95% CI 0.82–1.14; P = 0.6) for first AF/AFL recurrence. In both males and females, dronedarone treatment vs. placebo resulted in a significant reduction in the risk of first cardiovascular hospitalization or death due to any cause (HR 0.74, 95% CI 0.64–0.84; P < 0.00001 and HR 0.77, 95% CI 0.67–0.89; P = 0.0002, respectively) (Figure 3), driven by first cardiovascular hospitalization, and first AF/AFL recurrence (HR 0.85, 95% CI 0.77–0.94; P = 0.0017 and HR 0.71, 95% CI 0.64–0.80; P < 0.0001, respectively). There was no statistical difference in the risk of death due to any cause with dronedarone vs. placebo across age and sex subgroups.

A Cox regression interaction analysis identified no significant interaction between age and sex subgroups with regard to cardiovascular hospitalization or death due to any cause. The treatment differences identified above dominated the results independently for age and sex.

Safety
A summary of treatment-emergent adverse events (TEAEs) is included in Table 2. The incidence of TEAEs, including those leading to treatment discontinuation, increased with increasing age and was comparable across males and females. Overall, dronedarone was associated with a numerically higher incidence of TEAEs compared with placebo. Gastrointestinal disorders (primarily diarrhoea and
| Patient characteristics | Age subgroups | Sex subgroups |
|-------------------------|--------------|--------------|
|                         | <65 years    | ≥75 years    | Male          | Female        |
|                         | Dronedarone  | Placebo      | Dronedarone   | Placebo       |
|                         | (n = 431)    | (n = 442)    | (n = 907)     | (n = 978)     |
| Age, mean (SD) (years)  | 56.8 (6.2)   | 70.7 (2.6)   | 79.1 (3.7)    | 70.4 (9.5)    |
| Male, n (%)             | 269 (62.4)   | 464 (50.3)   | 437 (46.1)    | 1170 (100)    |
| Race, n (%)             | White        | Asian        | Black         | Other         |
|                         | 387 (89.8)   | 32 (7.4)     | 5 (1.2)       | 7 (1.6)       |
|                         | 405 (91.6)   | 19 (4.3)     | 13 (2.9)      | 5 (1.1)       |
|                         | 834 (90.4)   | 60 (6.5)     | 5 (0.5)       | 24 (2.6)      |
|                         | 806 (88.9)   | 71 (7.8)     | 10 (1.1)      | 20 (2.2)      |
|                         | 844 (89.1)   | 58 (6.1)     | 9 (1.0)       | 36 (3.8)      |
|                         | 861 (88.0)   | 64 (6.5)     | 8 (0.8)       | 45 (4.6)      |
|                         | 1042 (89.1)  | 84 (7.2)     | 13 (1.1)      | 31 (2.6)      |
|                         | 1145 (88.8)  | 98 (7.6)     | 15 (1.2)      | 31 (2.4)      |
| Weight, mean (SD) (kg)  | 91.1 (21.5)  | 92.9 (21.4)  | 80.9 (15.4)   | 74.6 (14.9)   |
|                         | 227 (52.7)   | 233 (52.7)   | 597 (65.8)    | 712 (75.2)    |
|                         | 204 (47.3)   | 209 (47.3)   | 318 (34.5)    | 235 (24.8)    |
|                         | 214 (49.6)   | 259 (58.6)   | 54 (5.8)      | 0             |
|                         | 217 (50.3)   | 183 (41.4)   | 725 (78.6)    | 727 (80.2)    |
|                         | 0            | 0            | 144 (15.6)    | 137 (15.1)    |
|                         | 1.6 (0.8)    | 1.4 (0.7)    | 2.7 (0.8)     | 2.7 (0.8)     |
| CHA2DS2-VASc score,a n (%) | 215 (50.4) | 228 (52.4) | 537 (58.9) | 554 (61.4) |
|                         | 84 (19.5)    | 95 (21.5)    | 266 (28.8)    | 277 (30.5)    |
|                         | 42 (9.7)     | 38 (8.6)     | 126 (13.7)    | 130 (14.3)    |
|                         | 33 (7.7)     | 31 (7.0)     | 26 (2.8)      | 20 (2.2)      |
|                         | 11 (2.6)     | 20 (4.5)     | 40 (4.3)      | 38 (4.2)      |
|                         | 384 (89.1)   | 399 (90.3)   | 818 (88.6)    | 816 (90.0)    |
|                         | 21 (4.9)     | 37 (8.4)     | 37 (4.0)      | 37 (4.1)      |
|                         | 16 (3.7)     | 19 (4.3)     | 82 (8.9)      | 78 (8.6)      |

*Derived a posteriori (not included in the primary analysis of the ATHENA study); mean [SD] CHA2DS2-VASc scores in the overall ATHENA population: dronedarone 2.9 [1.1] and placebo 2.8 [1.1].

1. Defined as coronary heart disease and/or ischaemic dilated cardiomyopathy and/or non-ischaemic dilated cardiomyopathy and/or rheumatic valvular heart disease and/or non-rheumatic valvular heart disease and/or congestive heart failure.

2. Data were missing in <2% of patients.

AF, atrial fibrillation; AFL, atrial flutter; BMI, body mass index; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischaemic attack (doubled), vascular disease, age 65–74 years, sex category: female; SD, standard deviation.
Discussion

ATHENA is the largest clinical trial assessing clinical outcomes with an antiarrhythmic drug. The majority of patients were aged 65 years or older. Patients aged <65 years comprised only 19% of the total patient population, due to amendments in the protocol to enrich the risk profile of the study population. The proportion of males and females was comparable in ATHENA. This post hoc analysis is thus ideally suited to explore differences in efficacy and safety by age and sex. In this analysis, dronedarone significantly reduced the risk of cardiovascular hospitalization or death and AF/AFL recurrence among patients aged 65–74 years and ≥75 years, compared with placebo. Among patients aged <65 years, the point estimate of the HR for cardiovascular hospitalization or death and AF/AFL recurrence among patients aged <65–74 years and ≥75 years, compared with placebo. Younger patients would be expected to have a lower burden of cardiovascular disease compared with older patients, which, along with a lower risk associated with younger age, would be reflected in less frequent cardiovascular hospitalizations. To this point, the incidence of first cardiovascular hospitalization or death due to any cause in the placebo arms was slightly lower in the <65 years subgroup compared with older age subgroups. Moreover, this group was only half as large as the other age subgroups owing to a change in inclusion criteria.
during the trial, as mentioned above. Thus, the power to detect a difference between the treatment arms was lower in this group, as reflected in the wider confidence intervals (being almost twice as wide as those in the other age groups) observed in the efficacy results.

In this analysis, cardiovascular hospitalization rates were numerically higher in females than in males. The efficacy of dronedarone vs. placebo was, however, maintained among both males and females. Mean age was higher in females and mean CHA2DS2-VASc scores indicating risk of stroke were higher in females compared with males by more than the expected point for sex. Nonetheless, the use of vitamin K antagonists such as warfarin was lower in females. Similar results were reported among patients in the PINNACLE registry, with a lower proportion of females with CHA2DS2-VASc scores ≥2 receiving oral anticoagulants vs. aspirin compared with males.13

Treatment-emergent adverse events associated with dronedarone as well as placebo increased with increasing age and were comparable among males and females. Dronedarone was associated with a numerically greater incidence of TEAEs compared with placebo. It is known that treatment with antiarrhythmic drugs leads to a higher rate of proarrhythmic events in females, including torsade de pointes.
arising from QT interval prolongation. Older patients are also at higher risk for proarrhythmia with antiarrhythmic drugs, potentially because of a lower rate of clearance of the drugs from the body and due to the increased prevalence of chronic kidney disease and concomitant structural heart disease. In the primary analysis of the ATHENA trial, dronedarone treatment was associated with prolongation of the QT interval compared with placebo, but only a single case of torsade de pointes was reported, in a 66-year-old female patient with multiple comorbidities, who still presented with ventricular arrhythmias months after dronedarone wash-out (data on file). In the present analysis, as expected, dronedarone treatment was associated with QT interval prolongation across age and sex subgroups. The extent of QTc interval (Bazett formula) prolongation was small overall and comparable across age and sex subgroups. Additionally, treatment discontinuation due to QT interval prolongation was relatively rare with dronedarone treatment across age and sex subgroups (<2%).

Overall, this analysis adds to evidence that advanced age and female sex should not be limiting factors for treatment with dronedarone among patients with AF/AFL. Indeed, the most recent European Society of Cardiology (ESC) guidelines for the management of AF recommend the use of dronedarone (Class I recommendation/Level of Evidence A) as long-term rhythm control treatment regardless of patient age or sex.

**Limitations**

This was a post hoc analysis, and as such, was not powered to evaluate outcomes by age and sex subgroups. Therefore, the results of this analysis should be considered exploratory. In addition, data on the type of AF/AFL (i.e. paroxysmal vs. persistent) and AF burden at

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**Figure 3** Kaplan–Meier unadjusted estimates of time to first cardiovascular hospitalization or death among (A) males and (B) females. BID, twice a day; CI, confidence interval.
baseline or thereafter were not available for patients in the ATHENA study. As previously mentioned, the subgroup including those aged <65 years was smaller than the other age subgroups and associated with fewer events, thus reducing the power to detect a change in this group.

Conclusions
In this post hoc analysis of the ATHENA trial, dronedarone significantly reduced the risk of cardiovascular hospitalization or death due to any cause and AF/AFL recurrence among patients aged 65 years and older, many of whom had cardiovascular comorbidities such as coronary heart disease. When examined by sex subgroups, both males and females demonstrated significant clinical benefit with dronedarone compared with placebo. The safety of dronedarone, including QTc interval prolongation, was similar across age and sex subgroups. Further prospective studies are warranted to confirm the results of this analysis, which supports the use of dronedarone for improvement of clinical outcomes in older patients and regardless of sex.

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Data availability
Qualified researchers may request access to patient level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi’s data sharing criteria, eligible studies, and process for requesting access can be found at https://www.clinicalstudydatarequest.com/.

Supplementary material
Supplementary material is available at Europace online.

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