








# International cohort study on the effectiveness of dronedarone and other antiarrhythmic drugs for atrial fibrillation in real-world practice (EFFECT-AF)

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## Aims

To evaluate the effectiveness and safety of dronedarone compared with other commonly used antiarrhythmic drugs (AADs) for preventing atrial fibrillation (AF) recurrences.

## Methods and results

An international observational cohort study in Germany, Spain, Italy, and the USA enrolling patients with AF receiving AAD therapy. Patients with New York Heart Association (NYHA) Class IV heart failure were excluded. Participants were followed for up to 18 months, regardless of discontinuation or subsequent AAD switches. Atrial fibrillation recurrence was captured by hospitalization, emergency room visit, or electrocardiogram-based documentation of AF. Confounding bias was controlled for in the analysis of AF recurrence using multivariate models of 19 variables for adjustment. A total of 1009 participants [mean age 67.2 (10.8) years, male to female ratio 1.3] were recruited from 170 centres, 693 (69%) of which were from across Europe and the remaining 316 (31%) from the USA. At the time of enrolment, participants were taking dronedarone (51%) or other AADs (49%) [flecainide or propafenone (42%), sotalol (11%), and amiodarone (47%)]. No significant differences in the risk of first confirmed AF recurrence with dronedarone vs. other AADs [crude hazard ratio (HR) 1.10 (95% confidence interval 0.85–1.42); adjusted HR 1.16 (0.87–1.55)] were found, irrespective of whether univariate or multivariate models were used. Reported safety events were in accordance with the known safety profile of dronedarone.

## Conclusion

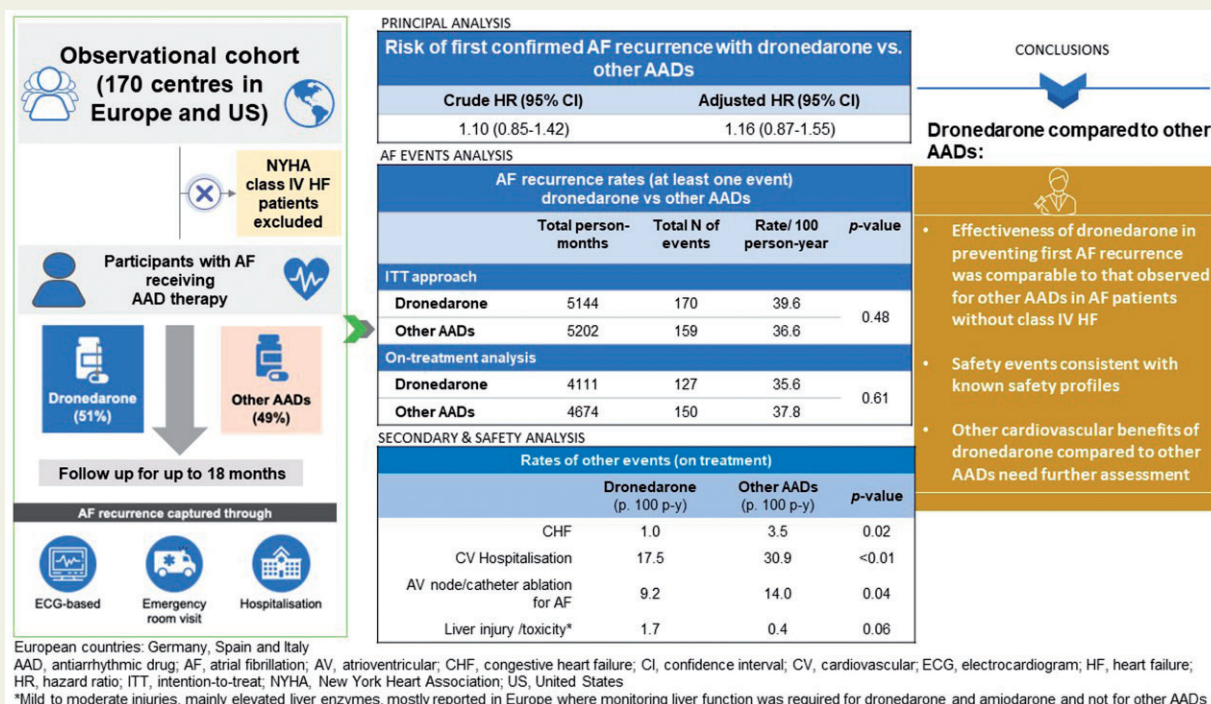
In this population of patients from either Europe or the USA receiving dronedarone or another AAD, the effectiveness of dronedarone was comparable to that observed for other AADs in preventing first AF recurrence.

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## Graphical Abstract



## Keywords

Atrial fibrillation • Dronedarone • Cardiovascular • Effectiveness • Safety • Cohort

## What's new?

- Findings reported here suggest that dronedarone has similar effectiveness to other commonly use antiarrhythmic drugs (AADs) for the prevention of paroxysmal and persistent atrial fibrillation recurrences in real-world settings.
- No significant differences in safety or liver toxicity were found with the use of dronedarone compared to other AADs under real-world circumstances.
- Similar to that found in pivotal studies, people on dronedarone showed a trend towards less cardiovascular hospitalizations and mortality in real-world practice although this was reported only in the on-treatment analysis.

## Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with reduced quality of life, cardiovascular (CV) morbidity, and mortality. Rhythm control therapy is indicated to improve

symptoms in patients with AF who remain symptomatic despite adequate rate control therapy<sup>1</sup> and is associated with a reduction in adverse CV outcomes.<sup>2</sup> Dronedarone is a multichannel blocker that works to control rhythm and rate in AF.<sup>3</sup> It meets the criteria of all four Vaughan-Williams antiarrhythmic drug (AAD) classes by inhibiting  $\beta$ -adrenergic receptors and blocking cardiac potassium channels, calcium, and sodium channels. Its approval was based on the outcomes of several randomized clinical trials.<sup>4-7</sup> The European Commission granted a marketing authorization<sup>8</sup> valid throughout the European Union for dronedarone on 26 November 2009, while dronedarone was approved in the USA on 1 July 2009.<sup>9</sup> In Europe, dronedarone is indicated to maintain sinus rhythm in adults with paroxysmal or persistent AF,<sup>8</sup> while in the USA, dronedarone is approved to reduce the risk of hospitalization due to AF in patients in sinus rhythm with a history of paroxysmal or persistent AF.<sup>9,10</sup> Dronedarone is contraindicated in patients with permanent AF based on the results of the PALLAS study,<sup>11</sup> similarly to other AADs. In the context of continuous evaluation of the benefit/risk of dronedarone, the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) requested that the marketing authorization holder should further evaluate and compare the

effectiveness and safety of dronedarone to that of other AADs in routine care.<sup>8</sup> Here, we report and discuss findings as per the original protocol.

## Study objective

The study's objective was to evaluate the effectiveness and safety of dronedarone compared with other commonly used AADs in the treatment of AF as prescribed by a cardiologist for preventing AF recurrences.

## Methods

This was an international observational multicentre cohort study conducted in hospitals and outpatient cardiology clinics across Germany, Spain, Italy, and the USA. The study population was composed of two cohorts of patients with paroxysmal or persistent AF,  $\geq 18$  years old, and prescribed (switched or started) dronedarone (50%) or other commonly used AAD (50%) (class IA/IC antiarrhythmics, sotalol, and amiodarone). Atrial fibrillation was considered to be paroxysmal if episodes terminated spontaneously within 7 days and persistent if electrical or pharmacological cardioversion was required for termination.<sup>12–15</sup> Patients with heart failure (HF) New York Heart Association (NYHA) Class IV or with permanent AF were excluded from the study. The cohort entry (index date) was defined as the earliest date of prescription of the index drug. The first prescription of an AAD (among naïve users, or 'starters') or the first prescription of another AAD after switching of AAD (among AAD 'switchers') was designated as the index AAD.

Data were collected by the treating cardiologists from medical charts and by the research team via telephone interviews of patients. All patients meeting the study eligibility criteria were assigned consecutively to the two, similar sized, cohorts (or strata); patients' outcomes at the time of recruitment were not known. Recruitment in each of the dronedarone/other AAD strata was continued until the target number of patients was reached. Patients were followed for up to 18 months with a minimum target of 12 months, regardless of discontinuation or subsequent switches to other AADs. Patient recruitment was conducted to ensure balanced recruitment of subjects on dronedarone and other AADs overall.

The outcome (AF recurrence) was categorized as recurrence/no recurrence, i.e. whether the outcome occurred at least once or not during each follow-up time window. In this study, only a confirmed AF recurrence was used as an outcome measure, meaning an AF recurrence that was confirmed by at least one of the following objective sources of information: hospitalization for AF, emergency room visit for AF, or electrocardiogram (ECG)-based report of AF, as reported by cardiologists in medical charts.

For assessing the risk [hazard ratio (HR)] of AF recurrence in patients taking dronedarone vs. other AAD, univariate and multivariate analyses were used. For the primary multivariate analysis, the 'intention-to-treat' time-varying Cox proportional hazards model was employed, with four follow-up time periods applied to patients (0–3 months; 4–6 months; 7–9 months; and 10 months end of follow-up). The AAD used at the start of the period was considered as a time-varying variable and applied to the whole period ('intention-to-treat' analysis). Only the first confirmed AF recurrence ('at least one event') was considered. For the secondary multivariate analysis, 'intention-to-treat' analysis using Cox proportional hazards model for the entire follow-up of participants and censoring at first confirmed AF recurrence (secondary multivariate analysis 1) or switch/discontinuation (secondary multivariate analysis 2) was used.

Confounding bias was controlled during the analysis of AF recurrence by adjusting within multivariate models for *a priori* and *a posteriori* identified potential confounders. Confounders were identified *a priori* by frequency distribution analysis at the index date of switching to or starting dronedarone or other AAD (with  $P < 0.1$ ). Variables used within the multivariate models were: age; sex; consumption of coffee and other caffeinated beverages (within 1 year before entering the study); left ventricular systolic dysfunction at index date; heart rate at index date; visit to cardiologist within 6 months before index date; history of HF-related comorbidities; history of thyroid disease/disorder; history of dermatological diseases; history of cardioversion; the presence of the implantable cardiac device at index date; history of hospitalization for CV reasons other than AF; and concomitant or past use of angiotensin-converting enzyme inhibitors, diuretics, medications for inflammatory diseases (including corticosteroids, immunosuppressants, or anti-TNF alpha agents), medications for diabetes, obesity, thyroid, and other endocrine conditions. In addition, variables to control for indication differences (AF type at diagnosis or at index date; recurrent AF attack since diagnosis; and switcher or starter at index date) and heterogeneity/differences in practice (country) were accounted for.

Further sensitivity analyses using different induction time/latency and carry-over effect time periods (30 days or 7 days after discontinuation) were conducted in an attempt to relate previous exposure to the outcome.

Unadjusted rates of other outcomes (events) of interest were calculated in order to analyse adverse outcomes: CV events, such as CV hospitalization, HF, myocardial infarction, progression to permanent AF, cerebrovascular accident/stroke; interstitial pulmonary disease; liver injury/toxicity; renal insufficiency/failure; and finally, mortality. The rates of these adverse outcomes were described as a number of at least one/first event per 100 person-years and presented by index drug taken at entry in the cohort ('intention-to-treat' analysis) and by a drug taken at time of the event (on-treatment analysis).

Investigators were instructed to complete a registry of non-included patients, i.e. potentially eligible subjects refusing to participate, not reached, or deceased. The register anonymously described participants by age (age group), sex (male/female), diagnosis (paroxysmal AF; persistent AF; both paroxysmal and persistent AF), medication use (dronedarone; other AADs), HF (NYHA Class I, II, or III or no HF), and reasons for non-participation (subject refused to participate; could not be reached; has passed away; withdrew consent), in accordance with the country-specific regulations. Participating and non-participating eligible subjects were compared on the available data in the registry of non-included patients, such as age, sex, diagnosis, and a confirmed HF diagnosis, to ensure that no bias was present.

All active sites in Europe and at least 20% of active sites in the USA underwent on-site monitoring with source data verifications during the study.

Ethical approval was obtained from the relevant institutional bodies in the participating countries. All included patients gave their informed consent to take part in the study.

## Declaration of Helsinki

The authors declare that the cohort study reported here complies with the Declaration of Helsinki and that the locally appointed ethics committee has approved the research protocol. The protocol and final report relating to the study presented here were subject to review and approval by the European Medicine Agency (EMA). An independent scientific committee that included the authors of the study reported here, oversaw the protocol, the conduct of the study, and its final report. Informed consent has been obtained from all included patients.

## Results

Out of a total of 1009 eligible patients from 170 centres in 4 countries, 693 (69%) patients were recruited in Europe and the remaining 316 (31%) in the USA. On average, each site recruited about 6 patients (ranging between 1 and 21) over the course of the study recruitment period (March 2013 to April 2014).

The analysis of the reasons for non-participation within the registry of non-included patients indicated that among those considered eligible for enrolment, the rate of non-participation was similar between patients taking dronedarone or another AAD: 73.3% vs. 73.5%, respectively. Overall, no significant differences were noted for either sex or mean age between the registry of non-included patients and eligible patients included in the study (results not shown).

The dronedarone cohort included 510 (50.5%) patients (67% starters—as initial antiarrhythmic treatment, and 33% switchers—after being switched from another AAD), while the ‘other AAD’ cohort included 499 (49.5%) patients (74% starters and 26% switchers) at study entry.

Among patients using other AADs, 232 (46.5%) were prescribed amiodarone, 210 (42.1%) flecainide or propafenone, 54 (10.8%) sotalol, and 3 (0.6%) other drugs (ajmaline and quinidine).

No significant differences by type of AF (paroxysmal vs. persistent) or distribution by switchers and starters were reported between the registry of non-included patients and that of participants in the study (results not shown).

### Baseline characteristics of patients

Overall, there was a similar distribution of key socio-demographic and other baseline characteristics between dronedarone and other AAD-treated patients (Table 1).

A higher proportion of patients on dronedarone had paroxysmal AF at index date compared to the remaining patients taking a different AAD (75.3% vs. 64.5%, respectively); whereas a lower proportion of patients taking dronedarone had persistent AF at index date (19.4% vs. 29.1%, respectively),  $P < 0.01$  (Table 1).

A lower proportion of patients taking dronedarone had a cardiac implantable electronic device at index date compared with patients on any other AAD: 8.6% vs. 14% ( $P = 0.01$ ). No significant differences between study groups were observed by education, employment status, occupation, living conditions, smoking, alcohol consumption, physical activity, or body mass index (Supplementary material online, Table S1).

Patients on dronedarone were similar to those on a different AAD for CV disorders such as hypertension, ischaemic disease, stroke, pulmonary embolism, arrhythmias other than AF, cardioversion, angioplasty, coronary bypass or other heart surgery, and other heart conditions except for cardiomyopathy which was less frequent in dronedarone users (6.7% vs. 11.1%,  $P < 0.01$ ) (Table 1, Supplementary material online, Table S2).

The proportion of patients who visited their cardiologist at least once within 6 months prior to study entry was higher in dronedarone users than other AADs users: 87.1% vs. 79.7% ( $P = 0.01$ ), respectively. There were no differences in the frequency of visits to general practitioners.

A higher proportion of dronedarone users had a history of thyroid disease/disorder than other AAD users: 15.2% vs. 9.3% ( $P = 0.01$ ).

No significant differences in the history of other non-CV comorbidities (renal, hepatic, or other) were observed between these two treatment groups (Table 1).

### Follow-up

The frequency of ECGs was compared between treatment groups. There were no significant differences in ECG availability between dronedarone or other AAD users, both at baseline and during each follow-up time frame: 85.9% vs. 85.6% at baseline ( $P = 0.89$ ); 76.9% vs. 79.2% at 3 months ( $P = 0.39$ ); 74.9% vs. 70.8% ( $P = 0.16$ ) at 6 months; and 85.9% vs. 84.1% ( $P = 0.46$ ) at 12 months, respectively. In addition, a similar proportion of dronedarone and other AAD users were followed-up at each time point: 96.9% vs. 98.2% at 3 months; 94.5% vs. 96.2% at 6 months; and 90.2% vs. 91% at 12 months, respectively.

### Primary outcome: confirmed atrial fibrillation recurrence

Table 2 shows the crude rate of first confirmed AF recurrence between patients taking dronedarone and other AADs, stratified by AAD starters and switchers.

There were no differences in AF recurrence rates between dronedarone and other AAD users when stratified by sex, age, and type of AF, and to where the subject was being treated (Europe or USA).

Table 3 displays univariate (non-adjusted) and multivariate (adjusted for the effect of potential confounders) models of the risk of first confirmed AF recurrence with dronedarone vs. other AADs. Results were similar regardless of the different Cox models used for time windows or censoring.

No statistically significant differences were observed in sensitivity analyses using different induction time/latency and carry-over effect time periods (30 days or 7 days) to relate previous exposure to the outcome (Supplementary material online, Table S3).

### Pre-specified adverse outcomes and overall adverse events

Data on pre-specified adverse CV, renal, or hepatic outcomes and mortality are presented in Table 4.

In the intention-to-treat analysis, no statistically significant differences ( $P < 0.05$ ) were observed regarding the occurrence of any of the outcomes listed in Table 4 between dronedarone and other AADs. Statistically significant differences observed in on-treatment analysis favoured dronedarone for CV hospitalization (17.5 vs. 30.9 per 100 person-year,  $P < 0.01$ ), congestive HF (1.0 vs. 3.5 per 100 person-year,  $P = 0.02$ ), and atrioventricular node ablation and catheter ablation for AF (9.2 vs. 14.0 per 100 person-year,  $P = 0.04$ ).

One patient treated with dronedarone was reported to have died during the study, but the death was not suspected to be related to dronedarone by the investigator (progressive pulmonary cancer); seven deaths were reported among patients treated with other AADs, of which one case of progressive respiratory failure was reported as suspected to be linked to the AF treatment (amiodarone). In the intention-to-treat analysis, no statistically significant differences were observed concerning the occurrence of death between dronedarone and other AADs. Statistically significant

**Table 1** Cohort demographics and other baseline characteristics

|  | Dronedarone at index date | Other AADs at index date | P-value |
|--|---------------------------|--------------------------|---------|
| Age at index date                                    |                           |                          |         |
| Mean (SD)  | 67.3 (10.4)               | 67.0 (11.3)              | 0.59    |
| Median (range)                                       | 68.5 (21.7–89.7)          | 68.0 (23.9–92.7)         |         |
| Sex  |                           |                          |         |
| Male   | 282 (55.3%)               | 297 (59.5%)              | 0.17    |
| Female   | 228 (44.7%)               | 202 (40.5%)              |         |
| Ethnicity  |                           |                          |         |
| Caucasian  | 393 (90.1%)               | 365 (88.8%)              | 0.53    |
| Other  | 43 (9.9%)                 | 46 (11.2%)               |         |
| Unknown  | 74                        | 88                       |         |
| History of cardiovascular comorbidities <sup>a</sup> |                           |                          |         |
| Yes  | 444 (88.6%)               | 434 (88.8%)              | 0.95    |
| No   | 57 (11.4%)                | 55 (11.2%)               |         |
| Unknown  | 9                         | 10                       |         |
| Hypertension   |                           |                          |         |
| Yes  | 387 (77.1%)               | 373 (75.5%)              | 0.81    |
| No   | 115 (22.9%)               | 121 (24.5%)              |         |
| Unknown  | 8                         | 5                        |         |
| Ischaemic heart disease                              |                           |                          |         |
| Yes  | 80 (16.4%)                | 90 (18.9%)               | 0.43    |
| No   | 408 (83.6%)               | 386 (81.1%)              |         |
| Unknown  | 22                        | 23                       |         |
| Stroke   |                           |                          |         |
| Yes  | 22 (4.5%)                 | 20 (4.1%)                | 0.94    |
| No   | 471 (95.5%)               | 465 (95.9%)              |         |
| Unknown  | 17                        | 14                       |         |
| Pulmonary embolism                                   |                           |                          |         |
| Yes  | 6 (1.2%)                  | 7 (1.5%)                 | 0.74    |
| No   | 487 (98.8%)               | 473 (98.5%)              |         |
| Unknown  | 17                        | 19                       |         |
| Cardioversion  |                           |                          |         |
| Yes  | 221 (45.2%)               | 250 (51.0%)              | 0.07    |
| No   | 268 (54.8%)               | 240 (49.0%)              |         |
| Unknown  | 11                        | 9                        |         |
| Coronary angioplasty                                 |                           |                          |         |
| Yes  | 54 (10.9%)                | 51 (10.6%)               | 0.86    |
| No   | 441 (89.1%)               | 432 (89.4%)              |         |
| Unknown  | 15                        | 16                       |         |
| Coronary bypass surgery                              |                           |                          |         |
| Yes  | 18 (3.6%)                 | 27 (5.6%)                | 0.14    |
| No   | 479 (96.4%)               | 456 (94.4%)              |         |
| Unknown  | 13                        | 16                       |         |
| Other heart surgery                                  |                           |                          |         |
| Yes  | 34 (6.8%)                 | 35 (7.3%)                | 0.76    |
| No   | 463 (93.2%)               | 442 (92.7%)              |         |
| Unknown  | 13                        | 22                       |         |
| Left ventricular systolic dysfunction                |                           |                          |         |
| Yes  | 36 (8.8%)                 | 55 (13.3%)               | 0.04    |
| No   | 374 (91.2%)               | 357 (86.7%)              |         |
| Unknown  | 100                       | 87                       |         |
| Cardiomyopathy                                       |                           |                          |         |
| Yes  | 33 (6.7%)                 | 53 (11.1%)               | <0.01   |

Continued

**Table I** Continued

|  | Dronedarone at index date | Other AADs at index date | P-value |
|--|---------------------------|--------------------------|---------|
| No   | 457 (93.3%)               | 427 (89.0%)              |         |
| Unknown  | 20                        | 19                       |         |
| History of heart failure (any NYHA class)                    |                           |                          |         |
| Yes  | 147 (30.0%)               | 168 (34.9%)              | 0.11    |
| No   | 343 (70.0%)               | 314 (65.1%)              |         |
| Not known  | 20                        | 17                       |         |
| History of heart failure (NYHA class III)                    |                           |                          |         |
| Yes  | 28 (5.7%)                 | 45 (9.4%)                | <0.01   |
| No   | 465 (94.3%)               | 434 (90.6%)              |         |
| Unknown  | 17                        | 20                       |         |
| History of other comorbidities (hepatic, renal, and other)   |                           |                          |         |
| Yes  | 354 (72.8%)               | 328 (68.9%)              | 0.18    |
| No   | 132 (27.2%)               | 18 (3.1%)                |         |
| Unknown  | 24                        | 23                       |         |
| Type of AF at index date                                     |                           |                          |         |
| Paroxysmal AF  | 384 (75.3%)               | 321 (64.5%)              | <0.01   |
| Persistent AF  | 99 (19.4%)                | 145 (29.1%)              |         |
| Both paroxysmal and persistent AF                            | 27 (5.3%)                 | 32 (6.4%)                |         |
| Unknown  | 0                         | 1                        |         |
| AF duration (between ECG confirmed diagnosis and index date) |                           |                          |         |
| Mean (in months)   | 11.7 (24.2)               | 9.2 (19.2)               | 0.12    |
| Median (in months)   | 1.2 (0–169.8)             | 0.8 (0–124.4)            |         |

AF, atrial fibrillation; ECG, electrocardiogram; NYHA, New York Heart Association; SD, standard deviation.

<sup>a</sup>Hypertension, heart failure, ischaemic heart disease, myocardial infarction, stroke, transient ischaemic attack, other vascular disease, rheumatic heart disease, haemodynamically significant valvular heart disease, second or third-degree atrioventricular block, complete bundle branch block, distal block, sinus node dysfunction, or atrial conduction defects, sick sinus syndrome, pre-excitation syndromes (e.g. Wolff–Parkinson–White), cardiomyopathy, pulmonary embolism, Raynaud's phenomenon and severe peripheral circulatory disturbances, Torsade de pointes, long QT syndrome, and other cardiovascular comorbidity.

differences observed in on-treatment analysis over death favoured dronedarone for death (0 vs. 1.08,  $P = 0.04$ ).

Nine liver injury/toxicity events were reported, all categorized as 'mild' or 'moderate' by investigators, including three events of 'liver injury' or 'hepatopathy' (two participants on dronedarone, one on another AAD), and six events of elevated liver enzymes (five participants on dronedarone, one on another AAD). Two hospitalizations for liver injury/toxicity events were reported (one in each treatment cohort), both classified as moderate. Most liver injuries were reported in Europe (seven cases in Germany, one case in Spain), and one case was reported in the USA. No statistically significant differences ( $P < 0.05$ ) were observed regarding the occurrence of liver injury/toxicity events between dronedarone and other AADs by the intention-to-treat or the on-treatment analysis.

Overall, 633 adverse events (AEs) were reported during the course of the study in 314 patients. Out of the 633 AEs, 204 (32.2%) were reported in patients treated with dronedarone (at time of the AE), 317 (50.1%) in patients treated with other AAD, and 111 (17.5%) reported for non-study drugs. Among these, 229 AEs were classified as serious: 63 serious events were reported in dronedarone users, 24 of which were suspected to be related to dronedarone, whereas 125 serious events were reported in other AADs users, 39 of which suspected to be related to the AF treatment.

## Discussion

To the best of our knowledge, the EFFECT-AF is the largest clinical epidemiology cohort study comparing the effectiveness of dronedarone vs. other AADs as routinely prescribed by cardiologists in their daily practice.<sup>16</sup> Also, the EFFECT-AF represents a large variety of real-world cardiology practices that manage AF patients, reflecting different treatment pathways of these patients in study countries (Germany, Spain, Italy, and the USA). In this study, dronedarone demonstrated similar effectiveness for preventing first AF recurrence compared with other AADs used in current clinical practice for AF rhythm control.

Dronedarone's ability to reduce the recurrence of AF and the CV burden of disease, including death, has been extensively studied in placebo-controlled clinical trials.<sup>4–7</sup> Although dronedarone was deemed less effective at decreasing AF recurrence compared to amiodarone in the DIONYSOS trial,<sup>17</sup> dronedarone demonstrated a more favourable safety profile in terms of thyroid and neurological AEs. The definition used for AF recurrence has been shown to influence study results. Whereas the DIONYSOS trial compared dronedarone vs. amiodarone with regards to AF recurrence in relation to cardioversion, in our study, we used a symptomatic clinical definition of AF recurrence based on hospitalization, emergency room admission, or ECG records of AF irrespective of cardioversion. We also

**Table 2 AF recurrence rates (at least one event) by dronedarone and other AADs**

|  | Total person-months | Total N of events | Rate, per 100 person-year | P-value |
|--|---------------------|-------------------|---------------------------|---------|
| All patients                           |                     |                   |                           |         |
| ITT approach <sup>a</sup>              |                     |                   |                           |         |
| Dronedarone                            | 5144                | 170               | 39.6                      | 0.48    |
| Other AADs                             | 5202                | 159               | 36.6                      |         |
| On-treatment analysis <sup>b</sup>     |                     |                   |                           |         |
| Dronedarone                            | 4111                | 127               | 35.6                      | 0.61    |
| Other AADs                             | 4674                | 150               | 37.8                      |         |
| Starters of first antiarrhythmic drugs |                     |                   |                           |         |
| ITT analysis <sup>a</sup>              |                     |                   |                           |         |
| Dronedarone (n = 341)                  | 3463                | 106               | 36.64                     | 0.79    |
| Other AADs (n = 371)                   | 3814                | 121               | 37.96                     |         |
| On-treatment analysis <sup>b</sup>     |                     |                   |                           |         |
| Dronedarone (n = 341)                  | 2950                | 79                | 32.05                     | 0.25    |
| Other AADs (n = 371)                   | 3364                | 107               | 38.06                     |         |
| Switchers of antiarrhythmic drugs      |                     |                   |                           |         |
| ITT analysis <sup>a</sup>              |                     |                   |                           |         |
| Dronedarone (n = 169)                  | 1681                | 64                | 45.56                     | 0.11    |
| Other AADs (n = 128)                   | 1388                | 38                | 32.77                     |         |
| On-treatment analysis <sup>b</sup>     |                     |                   |                           |         |
| Dronedarone (n = 169)                  | 1323                | 48                | 43.41                     | 0.46    |
| Other AADs (n = 128)                   | 1383                | 43                | 37.2                      |         |

AAD, antiarrhythmic drug; ITT, intention-to-treat.

<sup>a</sup>By index drug as exposure.

<sup>b</sup>By a drug taken at time of the event as exposure.

included patients with persistent and paroxysmal AF in our study, the results of which become more relevant to a broader AF population and not restricted to patients undergoing cardioversion. One should note that only about 10% of patients in the study population underwent catheter-based left atrial or surgical ablation, and subjects with long-standing persistent (>6 months) or permanent AF types were excluded. Finally, our study compared dronedarone to other AAD used in current practice and not only to amiodarone.

Few comparative studies on dronedarone in AF patients have been published. One randomized study demonstrated similar efficacy in preventing AF recurrences between dronedarone and propafenone.<sup>18</sup> An observational study demonstrating a lower risk of CV hospitalization with dronedarone than other AADs was conducted in the USA<sup>19</sup> (observed here for CV and renal failure hospitalizations). Another two observational studies were conducted in Europe, one demonstrating a lower risk of mortality with dronedarone compared to sotalol in Sweden<sup>20</sup> (observed here for dronedarone compared to other AADs in the on-treatment analysis), and the other a lower risk of stroke and myocardial infarction compared to other AADs in Germany<sup>21</sup> (not observed here). Lower rates of CV outcomes, such as CV hospitalizations and congestive HF, are reported in our study among patients taking dronedarone vs. other AADs. These findings, however, must be interpreted with caution, given the distribution of some CV characteristics of patients at baseline. Recently, the EAST-AFNET4 trial<sup>2</sup> demonstrated that early (<12 months of diagnosis), comprehensive rhythm control in patients with AF led to a significant reduction in a composite of CV mortality,

stroke, acute coronary syndrome, and HF hospitalization compared to guideline-based standard of care.

Overall, the frequency of AEs and serious AEs was lower with dronedarone than that observed with other AADs, but higher rates of mild to moderate liver injuries were observed during dronedarone use vs. other AADs. Liver injuries consisting of alterations in biological parameters were mostly reported in Europe, where monitoring liver function is required by European regulatory agencies for dronedarone users but no other AAD users. This regulatory requirement may have introduced an information bias against dronedarone that could partly explain the differences found. A case-referent study in Germany found class III AADs as a class to be associated with acute liver injury (elevated liver enzymes), with amiodarone displaying the highest odds ratio (OR) [5.90; 95% confidence interval (CI): 1.7–20.0] and an OR of 3.1 (95% CI: 0.7–14.8) for dronedarone. The same study reported a non-significant association for class I AADs with an OR of 2.08 (95% CI: 0.52–8.29).<sup>22</sup>

The difference found in the mortality rates, statistically significant in the on-treatment analysis and marginally non-significant in the intention-to-treat analysis, is aligned with results from ATHENA and AFFIRM trials. However, the observational nature of our study requires these findings to be interpreted with caution.

## Limitations

To fully reflect the findings reported here, some potential limitations need to be addressed. First, multiple potential confounders were

**Table 3 Overall hazard ratios (HRs) of confirmed AF recurrence between patients taking dronedarone and other AADs**

|   | Crude HR (95% CI) | Adjusted <sup>a</sup> HR (95% CI) |
|---|-------------------|-----------------------------------|
| Primary time-varying Cox proportional hazards model                           | 1.10 (0.85–1.42)  | 1.16 (0.87–1.55)                  |
| Secondary Cox proportional hazards model, censoring at the first event        | 1.09 (0.88–1.36)  | 1.11 (0.88–1.41)                  |
| Secondary Cox proportional hazards model, censoring at switch/discontinuation | 1.09 (0.84–1.41)  | 1.11 (0.83–1.48)                  |

AAD, antiarrhythmic drug; AF, atrial fibrillation; CI, confidence interval.

<sup>a</sup>Adjusted for age; sex; consumption of coffee and other caffeinated beverages (within 1 year before entering the study); left ventricular systolic dysfunction at index date; heart rate at index date; visit to cardiologist within 6 months before index date; history of heart failure-related comorbidities; history of thyroid disease/disorder; history of dermatological diseases; history of cardioversion; the presence of the implantable cardiac device at index date; history of hospitalization for cardiovascular reasons other than AF; and concomitant or past use of angiotensin-converting enzyme inhibitors, diuretics, medicines for inflammatory diseases (including corticosteroids, immunosuppressants, or anti-TNF alpha), medicines for the treatment of diabetes, obesity, thyroid, and other endocrine-related conditions.

**Table 4 Rates of pre-specified adverse outcomes (at least one event) by dronedarone and other AADs**

| Adverse outcomes                              | Dronedarone<br>(per 100 person-years) | Other AADs<br>(per 100 person-years) | P-value |
|---|---------------------------------------|--------------------------------------|---------|
| Cardiovascular hospitalization                |                                       |                                      |         |
| ITT analysis <sup>a</sup>                     | 21.9                                  | 27.6                                 | 0.09    |
| On-treatment analysis <sup>b</sup>            | 17.5                                  | 30.9                                 | <0.01   |
| Congestive heart failure                      |                                       |                                      |         |
| ITT analysis <sup>a</sup>                     | 1.5                                   | 3.5                                  | 0.05    |
| On-treatment analysis <sup>b</sup>            | 1.0                                   | 3.5                                  | 0.02    |
| AV node ablation and catheter ablation for AF |                                       |                                      |         |
| ITT analysis <sup>a</sup>                     | 12.1                                  | 12.2                                 | 0.96    |
| On-treatment analysis <sup>b</sup>            | 9.2                                   | 14.0                                 | 0.04    |
| Progression to permanent AF                   |                                       |                                      |         |
| ITT analysis <sup>a</sup>                     | 3.7                                   | 4.7                                  | 0.44    |
| On-treatment analysis <sup>b</sup>            | 3.2                                   | 3.9                                  | 0.59    |
| Myocardial infarction                         |                                       |                                      |         |
| ITT analysis <sup>a</sup>                     | 0                                     | 0.2                                  | 0.32    |
| On-treatment analysis <sup>b</sup>            | 0                                     | 0.2                                  | 0.35    |
| Interstitial pulmonary disease                |                                       |                                      |         |
| ITT analysis <sup>a</sup>                     | 0                                     | 0.4                                  | 0.16    |
| On-treatment analysis <sup>b</sup>            | 0.3                                   | 0.2                                  | 0.92    |
| Cerebrovascular accident/stroke               |                                       |                                      |         |
| ITT analysis <sup>a</sup>                     | 1.2                                   | 0.4                                  | 0.15    |
| On-treatment analysis <sup>b</sup>            | 0.5                                   | 0.4                                  | 0.90    |
| Renal insufficiency/failure                   |                                       |                                      |         |
| ITT analysis <sup>a</sup>                     | 0.8                                   | 1.7                                  | 0.17    |
| On-treatment analysis <sup>b</sup>            | 1.0                                   | 1.5                                  | 0.49    |
| Liver injury/toxicity                         |                                       |                                      |         |
| ITT analysis <sup>a</sup>                     | 1.3                                   | 0.4                                  | 0.09    |
| On-treatment analysis <sup>b</sup>            | 1.7                                   | 0.4                                  | 0.06    |
| Mortality                                     |                                       |                                      |         |
| ITT analysis <sup>a</sup>                     | 0.38                                  | 1.32                                 | 0.10    |
| On-treatment analysis <sup>b</sup>            | 0                                     | 1.08                                 | 0.04    |

AADs, antiarrhythmic drugs; AF, atrial fibrillation; AV, atrioventricular; ITT, intention-to-treat.

<sup>a</sup>By index drug as exposure.

<sup>b</sup>By a drug taken at time of the event as exposure.



assessed, reporting largely similar distribution between dronedarone and other AAD-treated participants in terms of the overall history of CV and other comorbidities, as well as by socio-demographic and behavioural lifestyle factors. Notwithstanding, and as expected, one notable difference observed related to the history of HF, left ventricular systolic dysfunction, and other heart muscle pathologies, such as cardiomyopathy. Following the publication of results from the PALLAS<sup>11</sup> and ANDROMEDA<sup>23</sup> studies, symptomatic HF with recent decompensation requiring hospitalization or NYHA Class IV HF became a contraindication for dronedarone in the USA, whereas history of, or current HF or left ventricular systolic dysfunction is a contraindication in Europe. Furthermore, in the USA, the FDA label warns on risk in patients with decompensated HF or permanent AF.

Confounding bias was controlled during analysis by adjusting within multivariate models, and in addition, variables to control for indication differences and heterogeneity/differences in practice were accounted for in the multivariate models too. Nevertheless, like for any other observational study, some residual, unmeasured confounding may remain.

Misclassification of exposure would occur if patients exposed to a drug were recorded as not exposed, or vice versa. The possibility of such bias is unlikely in this study, as the exposure information was provided by treating cardiologists based on information recorded within the cardiology charts. Indeed, when using the intention-to-treat approach, it is possible that patients classified as 'exposed' may not have been taking the AAD in question at the time of the event occurred, but that is the very nature of the 'intention-to-treat' analysis.

No noticeable difference was observed in the rate of events between intention-to-treat and on-treatment analyses, and the HRs were similar irrespective of intention-to-treat being used for the whole follow-up or only for periods of 3 months in the Cox-proportional hazard models. Also, the nature of the censoring event (recurrence or switch/discontinuation) did not affect the results noticeably, which militates against an indication bias during follow-up. Sensitivity analyses using different induction time/latency and carry-over effect time periods to relate exposure to the outcome did not change the observed results.

No indication of differential selection bias associated with the exposure status was observed when comparing participants and non-participants in the study (from the registry of non-included subjects). Likewise, no indication of lead time bias in the evaluation of the primary outcome measure—AF recurrence, was observed as the frequency of ECG and rates of follow-up were comparable between the two groups of dronedarone and other AAD-treated patients. However, undetected selection bias cannot be fully excluded in an observational study.

Analysis based on the date of AF recurrence was not feasible, as the exact date of AF recurrence was not known. Fixed periods for analysis based on follow-up time intervals were used instead. The outcome (AF recurrence) was categorized as recurrence/no recurrence (i.e. whether the outcome occurred at least once or not during each follow-up time window).

Given the subjective nature of some symptoms for AF recurrence, misdiagnosis is possible. For this reason, only confirmed AF recurrence was used in our study (i.e. AF recurrence confirmed by at least

one objective source of information: either hospitalization for AF, emergency room visit for AF, or ECG-based reports of AF). Therefore, it is likely that our study captured more severe instances of AF recurrence, which would require clinical confirmation as per one of the criteria listed above.

When assessing the possible impact of survival bias, the proportion of patients lost to follow-up at each visit was similar in both dronedarone and other AAD-treated cohorts. In addition, the analysis of the registry of non-included subjects indicated a comparable proportion of potentially eligible dronedarone and other AAD patients deceased at the time of identification and therefore included within the registry.

The higher frequency of visits to cardiologists suggests that patients receiving dronedarone were likely to be followed up more closely after being first prescribed this drug than those not receiving dronedarone treatment. This could have been caused by the more recent introduction of the drug and the resulting recommended surveillance programme. Such stricter monitoring could have led to earlier recognition of outcome events, because of differential monitoring process during follow-up<sup>24</sup> rather than differential effectiveness or safety, in patients who took dronedarone vs. other AAD. In fact, if such information bias occurred, it would act against the new drug (in this study—dronedarone) as the outcomes would be more likely detected in patients treated with dronedarone.

The strength of the study relies on its multicentre, prospective design, and the uniform data collection under routine clinical practice, comprising different care settings. The study was designed to compare dronedarone to regular practice and not to individual AADs that may have different efficacies (amiodarone, flecainide, and propafenone).

## Conclusion

In summary, it can be concluded that the EFFECT-AF cohort study contributes to the growing body of evidence to support the effectiveness and safety of dronedarone compared to other AADs in a real-world international setting including European countries and the USA. This historical prospective cohort study highlights a similar effectiveness profile for dronedarone in terms of preventing first AF recurrence as compared to other AADs. The reported AEs were in accordance with the known safety profile of dronedarone. Lower rates of CV outcomes, such as CV hospitalization and cardiac HF, were observed in the on-treatment-analysis, which must be interpreted with caution given the observational nature of our study.

## Supplementary material

Supplementary material is available at *Europace* online.

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## Data availability

Qualified researchers may request access to 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 for validation purposes. Only fully anonymized data will be provided, which may require aggregation of some patient-level variables.

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