Safety and efficacy of dronedarone from clinical trials to real-world evidence: implications for its use in atrial fibrillation

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Efficacy and safety of dronedarone was shown in the ATHENA trial for paroxysmal or persistent atrial fibrillation (AF) patients. Further trials revealed safety concerns in patients with heart failure and permanent AF. This review summarizes insights from recent real-world studies and meta-analyses, including reports on efficacy, with focus on liver safety, mortality risk in patients with paroxysmal/persistent AF, and interactions of dronedarone with direct oral anticoagulants. Reports of rapidly progressing liver failure in dronedarone-prescribed patients in 2011 led to regulatory cautions about potential liver toxicity. Recent real-world evidence suggests dronedarone liver safety profile is similar to other antiarrhythmics and liver toxicity could be equally common with many Class III antiarrhythmics. Dronedarone safety concerns (increased mortality in patients with permanent AF) were raised based on randomized controlled trials (RCT) (ANDROMEDA and PALLAS), but comedication with digoxin may have increased the mortality rates in PALLAS, considering the dronedarone–digoxin pharmacokinetic (PK) interaction. Real-world data on apixaban–dronedarone interactions and edoxaban RCT observations suggest no significant safety risks for these drug combinations. Median trough plasma concentrations of dabigatran 110 mg during concomitant use with dronedarone are at acceptable levels, while PK data on the rivaroxaban–dronedarone interaction are unavailable. In RCTs and real-world studies, dronedarone significantly reduces AF burden and cardiovascular hospitalizations, and demonstrates a low risk for proarrhythmia in patients with paroxysmal or persistent AF. The concerns on liver safety must be balanced against the significant reduction in hospitalizations in patients with non-permanent AF and low risk for proarrhythmias following dronedarone treatment.

Keywords: Atrial fibrillation • Dronedarone • Rhythm control • Interaction • Digoxin • Direct oral anticoagulants • Real world • Liver toxicity

Introduction

Dronedarone is a non-iodinated benzofuran developed specifically for the treatment of atrial fibrillation (AF), designed to retain the efficacy of amiodarone, but with an improved safety profile. Dronedarone was approved in the European Union (EU) for rate and rhythm control of AF in 2009, following placebo-controlled trials in patients with AF (EURIDIS, ADONIS, ERATO, and ATHENA), and in comparison to amiodarone (DIONYSOS). The ATHENA trial showed that dronedarone significantly reduced the composite...
The efficacy of dronedarone in maintaining sinus rhythm (SR) was shown in the ADONIS and EURIDIS trials, with dronedarone reducing the risk of adjudicated AF recurrence by 26% ($P = 0.02$) and 29% ($P = 0.006$) vs. placebo from day 5 to 12 months post-randomization, respectively. Rhythm control is an important factor for the quality of life (QoL) of patients with AF, therefore, it may be preferable compared with rate control. Along with this, the prospective, open-label IMPULS study showed that after 12 months of treatment with dronedarone in 342 patients with paroxysmal or persistent AF, QoL was improved vs. baseline by $+16.0 \pm 23.5$ points ($P < 0.0001$), as measured by the psychological domain of the AF-QoL questionnaire. The percentage of patients in SR increased from 44.6% at baseline to 70.2% at 12 months following dronedarone treatment. Similarly, in a recent observational study of 824 Taiwanese patients with paroxysmal or persistent AF, dronedarone improved QoL following 6 months of treatment, as demonstrated by an increase in total score from $67.5 \pm 15.1$ (baseline) to $74.6 \pm 11.5$ (6 months) in an AF Effect on Quality of Life questionnaire. Notably, two recent randomized controlled trials (RCT), CABANA and CAPTAF, found that catheter ablation resulted in greater improvements in QoL of patients with symptomatic AF compared with antiarrhythmic drug (AAD) therapy at 12 months, with the limitation that no sham-ablation procedure was performed in the AAD treatment arm. However, in the CAPTAF trial, it could be demonstrated that the greater improvement in QoL was directly related to a greater reduction in AF burden in the ablation vs. AAD arm.

While dronedarone was designed to have a better safety profile than amiodarone, results from RCTs identified safety concerns in selected patient populations. The ANDROMEDA study indicated that dronedarone was not safe in patients with recently decompensated severe heart failure (HF), and the PALLAS trial raised safety concerns in patients with permanent AF. These studies led to the contraindication of dronedarone in patients with permanent AF and in patients with symptoms of HF in the EU. The potential effects of dronedarone on liver function resulted in the European Medicines Agency (EMA) issuing warnings and requiring monthly liver function tests (LFT) for the first 6 months of treatment, followed by a reduced frequency thereafter. In addition, concerns were raised about potential drug–drug interactions between dronedarone and direct oral anticoagulants (DOAC).

### Table 1 Clinical trials investigating the safety and efficacy of dronedarone

| Endpoints       | Clinical trial | No. of patients | AF patient population                      | Controls            | Efficacy vs. placebo                                                                 |
|-----------------|----------------|-----------------|---------------------------------------------|---------------------|-------------------------------------------------------------------------------------|
| Rhythm-based    | DAFNE          | 270             | Paroxysmal/persistent                       | Placebo             | 55% relative risk reduction in time to first AF recurrence                           |
|                 | ADONIS         | 625             | Paroxysmal/persistent                       | Placebo             | 26% reduction in the risk of adjudicated AF recurrence from day 5 to 12 months post-randomization |
|                 | EURIDIS        | 612             | Paroxysmal/persistent                       | Placebo             | 29% reduction in the risk of adjudicated AF recurrence from day 5 to 12 months post-randomization |
|                 | DIONYSOS       | 504             | Persistent                                  | Amiodarone 600 mg od for 28 days, then 200 mg od for at least 6 months | Incidence of the composite primary endpoint was 75.1% vs. 58.8% with amiodarone after 12 months’ treatment 54.4% reduction in AF burden |
| Rate control-based | ERATO         | 174             | Permanent, resting heart rate $>80$ b.p.m.  | Placebo             | Reduction of mean ventricular rate by 11.7 b.p.m. after 14 days                    |
| Combined        | ANDROMEDA      | 627             | Systolic dysfunction, advanced CHF NYHA Class III or IV | Placebo             | Prematurely discontinued due to increased deaths ($n = 25$) in the dronedarone arm compared to placebo ($n = 12$) |
|                 | ATHENA         | 4628            | Elderly patients with paroxysmal or persistent | Placebo             | 0.76 HR in all-cause mortality or CV hospitalization                                |
|                 | PALLAS         | 3236            | Permanent                                   | Placebo             | 2.29-fold increase in primary composite endpoint (first stroke, systemic arterial embolism, myocardial infarction, or CV death) (95% CI 1.34–3.94; $P = 0.002$) |

AF, atrial fibrillation; bid, twice daily; b.p.m., beats per minute; CHF, congestive heart failure; CI, confidence interval; CV, cardiovascular; HR, hazard ratio.
New post-approval studies on the safety and efficacy of dronedarone have been completed, and the results of these studies and their place in the context of past trials is the subject of this review.

Safety of dronedarone

During a review of the benefit–risk balance of dronedarone with regards to liver safety, the results of the PALLAS trial were communicated. In this comprehensive review, the EMA concluded that there remained a positive benefit–risk balance for dronedarone treatment in patients with paroxysmal or persistent AF. However, dronedarone should neither be used in patients with permanent AF; nor in patients with HF of New York Heart Association (NYHA) functional Class IV, or NYHA Class II–III with recent decompensation requiring hospitalization or in the presence of left ventricular dysfunction (ejection fraction <35%).

Given the extensive clinical development programme,1–3 dronedarone was given a Class IA recommendation in the European Society of Cardiology (ESC) 2010, 2012, and 2016 guidelines, as well as the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) 2014 guidelines for prevention of symptomatic paroxysmal/persistent AF in patients without HF, and a Class III recommendation for use in patients with HF or permanent AF.16–19

In recent years, several real-world studies and a number of meta-analyses have been conducted on dronedarone and other AADs, which have further assessed the safety profile of dronedarone (Table 2). Figure 1 shows a timeline of the key dronedarone studies and milestones.

A report by the Cochrane Collaboration of 59 studies, 21 305 patients found that several AADs, including amiodarone, dronedarone, flecainide, and sotalol, were effective at preventing AF recurrence, but were also discontinued due to adverse events (AE) (Figure 2A). A significantly increased mortality rate was associated with sotalol treatment (number needed to treat to harm: 169; 95% CI 60–2068), but comparisons of mortality between other Class III AADs and placebo found no significant differences (Figure 2B). Trends towards increased mortality for amiodarone have also been found in a meta-analysis of RCTs studying amiodarone, dronedarone, flecainide, propafenone, and sotalol vs. placebo (odds ratio (OR) 2.17, 95% CI 0.63–7.51).21 On the contrary, in trials of paroxysmal or persistent AF, dronedarone has not shown any signals of increased mortality associated with its use.1,3,4

In a recent real-world study analysing data of 300 000 patients with AF from the Swedish patient registry, those prescribed dronedarone or flecainide had a significantly lower all-cause mortality than sotalol (HR 0.44, 95% CI 0.34–0.57 or HR 0.55, 95% CI 0.44–0.68, respectively), while dronedarone was the only AAD associated with a lower risk of ventricular proarrhythmia vs. sotalol (HR 0.58, 95% CI 0.37–0.90).23 However, these results should be interpreted with caution as an important limitation of the study is confounding by indication; drugs have been selected non-randomly by information available to the clinician. Although the author performed a frailty analysis, the full severity of the patient’s condition cannot be accounted for in the study.23

In the canine heart, dronedarone (and amiodarone) eliminates early afterdepolarization activity induced by sotalol and other Class III AADs known to cause QT-prolongation and torsades des pointes.34 Additionally, in RCTs, dronedarone has been shown to have low proarrhythmic potential. In the ATHENA trial, the incidence of ventricular arrhythmia was comparable with placebo,3 while there were no reported episodes of torsades de pointes with dronedarone in the dose-ranging study, DAFNE, nor in other pre-approval dronedarone trials (EURIDIS, ADONIS, ERATO, ANDROMEDA, and DIONYSOS).2–4,7,8 In the 2015 Cochrane report, only three AADs—amiodarone, dronedarone, and propafenone—did not significantly increase proarrhythmia vs. controls (Figure 2C).25 In a meta-analysis of RCTs investigating AADs vs. placebo, dronedarone was associated with the lowest rate of proarrhythmia, including bradycardia (OR 1.45, 95% CI 1.02–2.08).21

A recent retrospective analysis of the German IQVIA database (2010–2017) involved 3498 patients receiving a first prescription of dronedarone and 17 724 patients receiving a first prescription of other AADs (amiodarone, flecainide, propafenone, or sotalol). The authors found that dronedarone was associated with a decreased risk of myocardial infarction (HR 0.78, 95% CI 0.63–0.96; P = 0.020) and stroke (HR 0.84, 95% CI 0.71–0.99; P = 0.043) in patients with AF compared with other AADs.35 These results are consistent with data from the post hoc studies based on the ATHENA trial, which demonstrated that patients with AF receiving dronedarone had reduced risk of a first acute coronary syndrome and stroke vs. patients receiving placebo.35,36 The most likely mechanism by which dronedarone reduces the risk of stroke is by inhibition of AF and a slower ventricular rate.35 In addition, dronedarone has been shown to prevent microvascular flow alterations in the left ventricle during AF,37,38 and also reduce the size of myocardial infarctions in porcine models.39

Interactions between anticoagulant drugs and dronedarone

Interactions with direct oral anticoagulants

The risk of stroke is five-fold higher in patients with AF, and the risk reduction from anticoagulant therapy is approximately 65%.40 Treatment with DOACs is associated with a lower risk of life-threatening intracranial bleeding and AEs than the commonly used vitamin K antagonist warfarin.41–44 Clinical data are limited and there is a shortage of pharmacokinetic (PK)/pharmacodynamic (PD) data on the use of DOACs with dronedarone. An important consideration when evaluating interactions between DOACs and dronedarone is permeability glycoprotein (P-gp) inhibition. Permeability glycoprotein plays a key role in the export of drugs from cells in the small intestine, blood–brain barrier, kidney proximal tubule and hepatocytes, and protects against foreign substances. A number of drugs, such as dronedarone, are known P-gp inhibitors, and when co-administered with DOACs can result in increased DOAC concentrations, consequently increasing the risk for bleeding.45 Known interactions between DOACs and dronedarone are summarized in Supplementary material online, Table S1.

Interactions

Apixaban

There is no specific advice regarding the concomitant use of dronedarone with apixaban due to lack of PK/PD data.46 Recently, the clinical safety of apixaban when combined with dronedarone was
analysed in a Swedish registry study of patients with AF. Intracranial bleeding, bleeding leading to hospitalization, and fatal bleeding events were compared in two propensity-matched cohorts of 1681 dronedarone-treated patients with AF in combination with either apixaban or warfarin (2013–2016).28 Treatment according to label with apixaban 5 mg twice daily (bid) concomitantly with dronedarone was not associated with more bleeding events than a combination of warfarin and dronedarone (HR 0.66; P = 0.121) (Figure 3); however, the study did not possess the statistical power to show non-inferiority. Overall, major bleeding events in patients with AF treated with dronedarone and either warfarin or apixaban were rare.28 These observational data suggest that dronedarone is safe to use in combination with the standard dose of apixaban, but the study was not powered to demonstrate a reduction in major bleeding or better survival vs. warfarin, as in the randomized trial comparing the two drugs.47,48

Dabigatran
Dabigatran is currently contraindicated with dronedarone by the EMA based on a PK study of 16 healthy volunteers treated with 400 mg dronedarone and 150 mg dabigatran, where the plasma concentration of dabigatran was increased by 1.7-fold.49 In a recent real-world study, in a cohort of 33 patients with AF treated with 400 mg dronedarone and 110 mg dabigatran, the median trough plasma concentration of dabigatran was similar to that found with a dose of 150 mg dabigatran without concomitant use of dronedarone, which was used in the RE-LY trial.32,43 No formal PK/PD studies have been performed studying the interaction between dronedarone and dabigatran 110 mg bid.

Edoxaban
For the more recently approved DOAC, edoxaban, the potential interaction with dronedarone is deemed to be moderate based on data from the ENGAGE-AF study,41 and the summary of product characteristics.

| Meta-analysis | Studies analysed/registries used | Main conclusion |
|---------------|---------------------------------|-----------------|
| Piccini et al.20 | 9 RCTs (4 dronedarone, 4 amiodarone, 1 RCT for direct comparison analysis) | Dronedarone has fewer adverse effects than amiodarone but is less effective at maintenance of SR |
| Freemantle et al.21 | 39 RCTs (amiodarone, dronedarone, flecainide, propafenone, sotalol) | Dronedarone was associated with lowest rate of proarrhythmia among AADs |
| Dagres et al.22 | 4 RCTs (dronedarone) | Reduced risk of stroke or transient ischaemic attack with dronedarone in paroxysmal or persistent AF |
| Chatterjee et al.23 | 7 RCTs (dronedarone) | Increased all-cause mortality with use of dronedarone in a wide spectrum of populations |
| Hohnloser et al.24 | 7 RCTs (dronedarone) | Presence of permanent AF was most important predictor of CV death with dronedarone |
| Lafuente-Lafuente et al.25 | 59 RCTs (quinidine, disopyramide, aprindine, bidisomide, flecainide, propafenone, metoprolol, amiodarone, azimilide, dofetilide, dronedarone, sotalol) | Several class IA, IC, II and III drugs have a moderate effect on maintaining SR following conversion of AF |
| Diemberger et al.26 | 12 RCTs and 7 OBS (dronedarone) | Dronedarone use for prophylaxis of AF recurrences was not associated with increased risk of death |
| Friberg27 | Swedish patient register | Patients with AF prescribed dronedarone did not have an increased risk of death or liver disease compared with patients with AF not receiving dronedarone |
| Friberg28 | Swedish patient register | Major bleeding was rare in patients with AF treated with apixaban in combination with dronedarone |
| Friberg29 | Swedish patient register | Dronedarone had a significantly lower risk for pro-arrhythmic death than sotalol |
| Grimaldi-Bensouda et al.30 | PGRx surveillance system | Association in use of class III antiarrhythmic with onset of acute liver injury |
| Ehrlich et al.31 | German IQVIA database | Dronedarone was associated with lower risk of myocardial infarction and stroke vs. other AADs. No cases of toxic liver disease were reported in patients treated with dronedarone and other AADs |
| Mochalina et al.32 | Swedish national quality registry (AuriculA) | A lower dose of dabigatran used concomitantly with dronedarone did not increase the plasma concentration of dabigatran |

AAD, antiarrhythmic drug; AF, atrial fibrillation; CV, cardiovascular; OBS, observational study; RCT, randomized controlled trial; SR, sinus rhythm.
for edoxaban recommends using a half-dose [30 mg once a day (od)] when used with dronedarone.50 Edoxaban is the only DOAC that has been studied for use with dronedarone; an open-label, randomized, two-period, two-treatment crossover study of 34 healthy volunteers showed that co-administration of edoxaban with dronedarone increased the edoxaban 24 h plasma concentration by 158%, while amiodarone decreased the 24 h plasma concentration of edoxaban by 26%. As a previous pharmacometric analysis predicted that increased edoxaban exposure associated with dronedarone would result in significant bleeding,51 the results of this study suggested that prescribing edoxaban without dose reduction presents a potential risk of bleeding in patients receiving dronedarone.52

Rivaroxaban

There is no specific advice for the concomitant use of dronedarone with rivaroxaban due to shortage of PK/PD data.46 However, in a recent study of 23 patients with paroxysmal AF for 9.1 ± 6.7 months, concomitant use of dronedarone and rivaroxaban was not associated with significant AEs.53

Figure 1 Timeline of key milestones for dronedarone. ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; EMA, European Medicines Agency; FDA, Food and Drug Administration; HF, heart failure; HRS, heart rhythm society; RWE, real-world evidence.

Figure 2 Withdrawals (A), overall mortality (B), and proarrhythmia (C) reported in clinical trials for antiarrhythmic drugs. Reproduced with permission and modified from Lafuente-Lafuente et al.25 aOdds ratio calculated by random effects model, as test for heterogeneity between pooled studies was significant. Some studies compared more than two drugs, so the total number of studies and patients in the figure is higher than the absolute number of studies and patients included. CI, confidence interval.
with dronedarone in a recent small study.\textsuperscript{53} Despite the lack of PK/PD studies, recent real-world data on combined therapy with the standard dose of apixaban suggested concomitant use of dronedarone and apixaban was not associated with significant safety risks when compared with dronedarone in combination with warfarin.\textsuperscript{58}

**Interactions with vitamin K antagonists**

The enzymes CYP2C9, CYP3A4, and CYP1A2 are the main routes of metabolism for warfarin; their inhibition increases the international normalized ratio (INR) and the risk of bleeding, requiring a lower dose of warfarin when amiodarone is administered.\textsuperscript{55} Dronedarone does not significantly inhibit CYP2C9 but is a moderate inhibitor of CYP3A4, while amiodarone, in comparison, interferes substantially with warfarin treatment by inhibiting CYP2C9, CYP3A4, and CYP1A2. In the DIONYSOS study, a smaller proportion of patients receiving dronedarone had supratherapeutic INR levels vs. patients receiving amiodarone, suggesting that dronedarone had fewer interactions with oral anticoagulants than amiodarone.\textsuperscript{15} For other CYP2C9 and CYP1A2 substrates, no interactions have been observed with dronedarone.

In 2009, the dronedarone briefing document submitted to the Food and Drug Administration (FDA) reported no safety concerns regarding drug–drug interactions of dronedarone with warfarin, as no clinically significant PK interaction was observed between the two drugs.\textsuperscript{56} International normalized ratio elevations have been reported in post-marketing cases in warfarin-treated patients initiated on dronedarone, and the EMA recommends monitoring INR levels following initiation with dronedarone when treated concomitantly with warfarin.\textsuperscript{57}

**Concomitant use of digoxin with dronedarone**

Digoxin treatment itself may be associated with an increase in all-cause mortality in patients with AF, as found in a retrospective analysis of the ROCKET-AF trial,\textsuperscript{42} and when used for rate control in patients with AF with or without HF in the AFFIRM study.\textsuperscript{58} Similarly, in a systematic review and meta-analysis of the literature (1993–2014) on digoxin-associated mortality, digoxin was associated with a 29\% increased mortality risk in the subgroup of 235 047 patients with AF compared with those patients not receiving digoxin (HR 1.29, 95\% CI 1.21–1.39; \textit{P} < 0.01).\textsuperscript{59} An updated systematic review and random-effect meta-analysis on publications up to March 2018 confirmed these results. New digoxin users (n = 41 687) showed an even higher risk for all-cause mortality vs. patients not receiving cardiac glycosides (HR 1.47; 95\% CI 1.15–1.88; \textit{P} < 0.01).\textsuperscript{60} These data suggest that digoxin use is associated with an increased mortality risk, especially for patients with AF.

Although several studies suggested dronedarone had a better safety profile than amiodarone—presenting a low risk of proarythmia, in both the ANDROMEDA and PALLAS trials—negative effects of dronedarone were seen in patients with severe chronic HF and depressed left ventricular systolic function.\textsuperscript{8} Increased mortality was seen in the PALLAS trial [21 deaths from CV causes in the dronedarone group and 10 deaths in the placebo group (HR 2.11; 95\% CI 1.00–4.49; \textit{P} = 0.046), including 13 deaths from arrhythmia in the dronedarone group and 4 deaths in the placebo group (HR 3.26, 95\% CI 1.06–10.00; \textit{P} = 0.03)], but a significant number of these patients were treated with digoxin concomitantly with dronedarone.\textsuperscript{9,61} A PK interaction is known to exist between dronedarone and digoxin. As a P-gp inhibitor, dronedarone reduces the renal excretion of digoxin, increasing its serum concentration to toxic levels.\textsuperscript{45} Also, a study on experimental models comparing concomitant use of dronedarone and amiodarone with the digitals glycoside ouabain in rabbits found that ouabain mediated a shortening of the ventricular refractory period, opposing the antiarrhythmic increases induced by dronedarone or amiodarone.\textsuperscript{62} Ouabain treatment together with dronedarone resulted in greater ventricular vulnerability to malignant ventricular arrhythmias compared with rabbits treated with a combination of ouabain and amiodarone, which also demonstrated an

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**Figure 3** Hazard ratios for bleeding outcomes with apixaban–dronedarone and warfarin–dronedarone combinations. Reproduced with permission from Friberg.\textsuperscript{28} CI, confidence interval; GI, gastrointestinal.
increased risk of proarrhythmia.\textsuperscript{62} In line with these findings, a case report showed that the combination of amiodarone and digoxin resulted in torsades de pointes in a patient with tachycardiomyopathy and no coronary artery disease.\textsuperscript{63}

Hence, PK/PD data and experimental animal data support that in combination with dronedarone, digoxin may be harmful and should be avoided. In line with the above data, in a retrospective analysis of the PALLAS trial, concomitant digoxin use had a significant effect on the hazard of dronedarone on all-cause mortality and arrhythmic death in patients with permanent AF (Table 3). The study suggests that the interaction between dronedarone and digoxin was responsible, in part, for most of the increased arrhythmic mortality observed in the PALLAS trial.\textsuperscript{64}

Although the PALLAS trial demonstrated an increased risk of mortality, based on real-world data, there are no signs of increased mortality associated with dronedarone treatment vs. control. Specifically, an analysis of the Swedish Drug Prescription Register found that mortality rates (unadjusted) were lower for dronedarone-treated patients with AF (1.3%, 95% CI 1.1–1.6) than control patients (14.0%, 95% CI 13.9–14.2; \(P < 0.0001\)), including patients with a history of HF. Following propensity score matching and adjustment for cofactors (previous and current diseases and medication), dronedarone-treated patients still demonstrated lower mortality than other patients with AF (HR 0.41, 95% CI 0.33–0.51).\textsuperscript{27} However, as mentioned previously, these real-world data should be interpreted with caution.\textsuperscript{13}

To conclude, there are divergences in the safety profile of dronedarone between RCTs and real-world observational studies, and concomitant use of digoxin in RCTs may play a significant part in this disparity.

### Data on liver safety

Although no concerns were raised about liver toxicity associated with dronedarone use in RCTs, in 2011, two reported cases of severe liver injury requiring organ transplantation prompted the EMA to perform a comprehensive review of all available data on potential liver toxicity caused by dronedarone. As a result, new warnings and precautions were introduced in the summary of product characteristics for dronedarone, and frequent LFTs were recommended.\textsuperscript{15} Currently, the strategies employed by the FDA and EMA to monitor potential liver toxicity associated with dronedarone use differ substantially (Figure 4), and compared with the FDA, the EMA’s regulations are more restrictive regarding LFTs for dronedarone-treated patients.\textsuperscript{65}

Recent experimental data suggest that amiodarone- and dronedarone-induced hepatotoxicity may occur through a similar mechanism, specifically the inhibition of mitochondrial fatty acid \(\beta\)-oxidation,\textsuperscript{66} and that, due to the lower lipophilicity of dronedarone compared with amiodarone, only specific patients may reach a high enough hepatic concentration of dronedarone to lead to hepatocyte damage.\textsuperscript{66}

In a previously unpublished analysis of liver safety, based on data from five RCTs studying dronedarone in patients with paroxysmal or persistent AF (DAFNE, EURIDIS, ADONIS, ERATO, and ATHENA), no statistically significant difference was found in hepatobiliary disorders reported between dronedarone and placebo. A greater percentage of patients experienced hepatic events with dronedarone treatment than placebo when time to first hepatic event or an alanine aminotransferase (ALT) \(\geq 5\times\) upper limit of normal (ULN) were analysed (dronedarone 400 mg bid: 3.4%, \(N = 3531\); placebo: 2.6%, \(N = 2875\)). However, no significant difference was found in the number of hepatic events between dronedarone and placebo when time to first serious hepatic event was examined (dronedarone 400 mg bid: \(n = 97\), \(N = 3282\); placebo: \(n = 74\), \(N = 2875\); \(P = 0.2566\)) (Table 4).

Focusing on post-marketing data, the Pharmacoepidemiologic General Research Extension study on acute liver injury cases (de novo elevation of liver enzymes) found an association between the use of Class III antiarrhythmics and onset of acute liver injury, mainly driven by amiodarone, demonstrating a greater risk (adjusted OR 5.90, 95% CI 1.7–20.0; \(P = 0.0044\)) than dronedarone (adjusted OR 3.13, 95% CI 0.7–14.8; \(P = 0.1505\)). The risk associated with Class I AADs was not statistically significant (adjusted OR 2.08, 95% CI 0.52–8.29; \(P = 0.2970\)).\textsuperscript{10} The recent, prospective, comparative cohort EFFECT-AF trial found that the rate of liver injury/toxicity among

### Table 3 All-cause mortality and arrhythmic deaths according to baseline digoxin use in a subgroup analysis of the PALLAS trial\textsuperscript{64}

| Outcome | Placebo | Dronedarone | Dronedarone vs. placebo |
|---------|---------|-------------|-------------------------|
|         | Events/N | Number of events/100 patient-months$^a$ | Events/N | Number of events/100 patient-months$^a$ | HR | 95% CI | \(P\) value |
| All-cause mortality (interaction \(P = 0.02\)) | 13/1617 | 0.2 | 25/1619 | 0.39 | 1.94 | 0.99–3.79 | 0.05 |
| No digoxin | 10/1091 | 0.23 | 8/1075 | 0.19 | 0.82 | 0.32–2.08 | 0.67 |
| Digoxin at baseline | 3/526 | 0.15 | 17/544 | 0.81 | 5.47 | 1.60–18.66 | 0.007 |
| Arrhythmic death (interaction \(P = 0.002\)) | 4/1617 | 0.06 | 13/1619 | 0.21 | 3.26 | 1.06–10.00 | 0.04 |
| No digoxin | 4/1091 | 0.09 | 2/1075 | 0.05 | 0.51 | 0.09–2.76 | 0.43 |
| Digoxin at baseline | 0/526 | 0.0 | 11/544 | 0.53 | 22.70$^b$ | 1.33–386.17$^b$ | 0.03 |

$^a$Total number of events/total patient-months \(\times 100\).

$^b$Risk was estimated as an odds ratio from a logistic regression with 0.5 added to each group.

CI, confidence interval; HR, hazard ratio.
Safety and efficacy of dronedarone from clinical trials to real-world evidence

Table 4  Liver safety data from clinical trials with dronedarone

| Parameter                  | PCSA criteria | Placebo  | Dronedarone 400 mg bid | Dronedarone 600 mg bid | Placebo  | Dronedarone 800 mg bid | Amiodarone 600 mg/200 mg od bid |
|----------------------------|---------------|----------|-------------------------|-------------------------|----------|------------------------|---------------------------------|
| ALT (SGPT-ALAT)            | >2 × ULN      | 34/559 (6.1%) | 86/1227 (7.0%)          | 16/66 (24.2%)           | 6/56 (10.7%) | 34/254 (13.4%)        |                                 |
|                            | >3 × ULN      | 11/559 (2.0%) | 35/1227 (2.9%)          | 3/66 (4.5%)            | 2/56 (3.6%) | 10/254 (3.9%)        |                                 |
|                            | >5 × ULN      | 5/559 (0.9%)  | 10/1227 (0.8%)          | 1/66 (1.5%)            | 0/56 (0.0%) | 2/254 (0.8%)        |                                 |
| AST (SGOT-ASAT)            | >2 × ULN      | 16/558 (2.9%) | 40/1227 (3.3%)          | 1/66 (1.5%)            | 1/56 (1.8%) | 14/254 (5.5%)        |                                 |
|                            | >3 × ULN      | 6/558 (1.1%)  | 14/1227 (1.1%)          | 1/66 (1.5%)            | 0/56 (0.0%) | 3/254 (1.2%)        |                                 |
|                            | >5 × ULN      | 0/558 (0.0%)  | 8/1227 (0.7%)           | 0/66 (0.0%)            | 0/56 (0.0%) | 2/254 (0.8%)        |                                 |

Overview of patients with hepatic event (AE or ALT ≥5 × ULN)

| Parameter                  | N = 2875 | Placebo  | Dronedarone 400 mg bid | Dronedarone 600 mg bid | Placebo  | Dronedarone 800 mg bid | Amiodarone 600 mg/200 mg od bid |
|----------------------------|----------|----------|------------------------|-------------------------|----------|------------------------|---------------------------------|
| TEAEs                      | 74 (2.6%) | 119 (4.1%) | 4 (6.1%)               | 2 (3.2%)               | 14 (5.5%) |                                 |                                 |
| Serious TEAEs              | 33 (1.1%) | 39 (1.1%) | 1 (1.5%)               | 0 (0.0%)               | 3 (1.2%) |                                 |                                 |
| AEs leading to premature study drug discontinuation | 7 (0.2%) | 17 (0.5%) | 0 (0.0%)               | 0 (0.0%)               | 6 (2.4%) |                                 |                                 |
| Serious TEAEs leading to hospitalization | 26 (0.9%) | 28 (0.8%) | 0 (0.0%)               | 0 (0.0%)               | 2.8% |                                 |                                 |
| Serious TEAEs leading to death | 2 (<0.1%) | 1 (<0.1%) | 0 (0.0%)               | 0 (0.0%)               | 0 (0.0%) |                                 |                                 |

Unadjusted analysis of time from randomization to first hepatic event or ALT ≥5 × ULN during the on-treatment period

| Parameter                  | Placebo  | Dronedarone 400 mg bid | Dronedarone 800 mg bid | Amiodarone 600 mg/200 mg od bid |
|----------------------------|----------|------------------------|-------------------------|---------------------------------|
| Median survival (95% CI) (months) | NC (NC to NC) | NC (NC to NC) | NC (NC to NC) | |
| Cumulative incidence of events (95% CI) | 0.013 (0.009–0.018) | 0.022 (0.016–0.028) | 0.040 (0.030–0.050) | 0.013 (0.009–0.018) |
| Log-rank test P-value | – | 0.2566 | 0.039 (0.031–0.047) | 0.016 (0.012–0.020) |
| Relative risk (95% CI) | – | 1.018 (0.749–1.385) | 0.007 (0.007–0.009) | – |

Figure 4 Differences in LFT regulations of EMA for amiodarone and dronedarone. EMA, European Medicines Agency; LFT, liver function test.

Parameter PCSA criteria

- ALT > 2 × ULN
- AST > 3 × ULN
- ALT > 5 × ULN
- AST > 5 × ULN

N = 564

Placebo: 34/559 (6.1%)
Dronedarone 400 mg bid: 86/1227 (7.0%)
Dronedarone 600 mg bid: 16/66 (24.2%)
Dronedarone 800 mg bid: 6/56 (10.7%)
Amiodarone 600 mg/200 mg od bid: 34/254 (13.4%)

Placebo: 11/559 (2.0%)
Dronedarone 400 mg bid: 35/1227 (2.9%)
Dronedarone 600 mg bid: 3/66 (4.5%)
Dronedarone 800 mg bid: 2/56 (3.6%)
Amiodarone 600 mg/200 mg od bid: 10/254 (3.9%)

Placebo: 5/559 (0.9%)
Dronedarone 400 mg bid: 10/1227 (0.8%)
Dronedarone 600 mg bid: 1/66 (1.5%)
Dronedarone 800 mg bid: 0/56 (0.0%)
Amiodarone 600 mg/200 mg od bid: 2/254 (0.8%)

Placebo: 16/558 (2.9%)
Dronedarone 400 mg bid: 40/1227 (3.3%)
Dronedarone 600 mg bid: 1/66 (1.5%)
Dronedarone 800 mg bid: 1/56 (1.8%)
Amiodarone 600 mg/200 mg od bid: 14/254 (5.5%)

Placebo: 6/558 (1.1%)
Dronedarone 400 mg bid: 14/1227 (1.1%)
Dronedarone 600 mg bid: 1/66 (1.5%)
Dronedarone 800 mg bid: 0/56 (0.0%)
Amiodarone 600 mg/200 mg od bid: 3/254 (1.2%)

Placebo: 0/558 (0.0%)
Dronedarone 400 mg bid: 8/1227 (0.7%)
Dronedarone 600 mg bid: 0/66 (0.0%)
Dronedarone 800 mg bid: 0/56 (0.0%)
Amiodarone 600 mg/200 mg od bid: 2/254 (0.8%)

*All randomized and treated patients with AF/AFL excluding patients from the ATHENA trial.

**All randomized and treated patients in AF/AFL studies (DAFNE, EURIDIS, ADONIS, ATHENA, ERATO, and DIONYSOS).

2 All randomized and treated patients with AF/AFL excluding patients from the DIONYSOS trial.

Kaplan–Meier estimates.

Relative risk (95% CI) adjusted on studies using Cox model.

Hazard ratio adjusted on studies using Cox model.

AE, adverse event; AF, atrial fibrillation; AFL, atrial flutter; ALT, alanine transaminase; AST, aspartate transaminase; bid, twice a day; CI, confidence interval; NC, not calculated; od, once daily; PCSA, potentially clinically significant abnormalities; SGOT-ASAT, serum glutamic oxaloacetic transaminase-aspartate aminotransferase; SGPT-ALAT, serum glutamic-pyruvic transaminase-alanine aminotransferase; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.
dronedarone-treated patients was only numerically higher than patients treated with other AADs (1.33/100 person-years vs. 0.38/100 person-years; \( P = 0.0936 \)), and most of the cases of liver injury/toxicity in dronedarone-treated patients were non-serious reports of liver enzyme increases. There were two hospitalizations for liver toxicity events (one in the dronedarone group and one in the other AADs group) and both were classified as moderate. Based on the different regulatory requirements regarding LFTs for dronedarone and other AADs (Figure 4), it is likely that a greater number of LFTs were conducted on dronedarone-treated patients during the study period vs. amiodarone.67 Data from a post hoc analysis from the DIONYSOS trial demonstrate a similar frequency of ALT/aspartate transaminase elevations in LFTs between dronedarone- and amiodarone-treated patients (Figure 5). These findings suggest that there might not be a need for more stringent, systematic liver enzyme measurements via LFTs in patients who receive dronedarone vs. those who receive amiodarone.

Real-world studies published since 2012 indicate there are no safety issues regarding serious liver damage with dronedarone. In the recent retrospective analysis of the German IQVIA database (2010–2017), which included patients initiated on dronedarone or other AADs (amiodarone, flecainide, propafenone, or sotalol), there were no reported cases of toxic liver disease in either group. In dronedarone patients, gamma-glutamyl transferase changed from 45.5 to 41.6 IU/L, while in patients treated with other AADs it changed from 52.2 to 48.1 IU/L. There was no significant difference between the two groups when comparing the value changes prior to and after the index date (\( P = 0.185 \)).31 A retrospective cohort study of an electronic medical record and an administrative claims data source (2009–14) found no evidence of increased risk of serious liver disease or interstitial lung disease in patients with AF treated with dronedarone vs. other AADs.68 In the analysis of the Swedish patient register (300 000 patients with AF), the incidence of new liver disease was low in all drug cohorts (dronedarone: 0.18/100 person-years at risk; amiodarone: 0.32/100 person-years at risk), and similar to that of patients with AF not treated with AADs (0.29/100 person-years at risk).29

Importantly, there is evidence suggesting that elevations in liver enzymes may occur regularly in patients with AF in routine clinical care—a probable result of their comorbidities and concomitant medication. In a retrospective study of 2151 patients with AF, the incidence of elevations of new ALT >2 × ULN was 2.1/100 person-years, and nearly all of the new elevated ALT measurements in the study were transient.69 Similarly, in the RE-LY trial, ALT levels >3 × ULN were found in 2.1% and 2.2% of patients treated with dabigatran or warfarin, respectively,43 suggesting that transient elevated ALT is common among patients with AF. Consequently, it may be difficult to correctly identify drug-induced increases in LFTs, particularly in the setting of new drug trials.69

Consequently, the data suggest that the rate of liver events associated with dronedarone use is comparable or lower than that observed for other AADs, and the EMA recommendations for LFTs do not reflect the whole body of evidence (clinical trials and real-world studies) presented here. There are also relevant differences between the FDA and EMA recommendations for LFTs (Table 5), where the recommended multiple LFTs during initiation of treatment with dronedarone in Europe may be perceived as overcautious.

**Efficacy**

**Hospitalization**

In a retrospective, real-world practice cohort study in 5656 patients with AF or atrial flutter, CV-related and AF-related hospitalization rates decreased by 41–45% (\( P < 0.0001 \)) with dronedarone treatment vs. baseline, and all-cause hospitalization was significantly reduced by 39%.70 In addition, in a retrospective study using the US Department of Defense electronic health record database between
2009 and 2011, dronedarone-treated patients with AF demonstrated significantly lower rates of CV hospitalizations and/or death from any cause compared with patients treated with other AADs (HR 1.24, 95% CI 1.05–1.47; \( P = 0.011 \)). Similar results were demonstrated for most CV outcomes, apart from non-hospitalized cardioversion, which was significantly lower with other AADs than with dronedarone (HR 0.81, 95% CI 0.71–0.92; \( P = 0.001 \)).71 These results are consistent with the ATHENA trial,1 demonstrating the effect of dronedarone on CV hospitalizations and mortality vs. placebo, along with lower mortality rates vs. other AADs.

**Atrial fibrillation burden**

The efficacy of dronedarone was also explored in relation to AF burden in the HESTIA trial. Relative AF burden, assessed through dual-chamber pacemakers, was reduced by 59% in patients who received dronedarone vs. placebo (absolute reduction in AF burden of 5.5% in the dronedarone group and increase of 1.1% in the placebo group).5 In addition, in a retrospective analysis of the EURIDIS and ADONIS trials, dronedarone decreased the risk of AF recurrences by 30.4% vs. placebo in patients without permanent AF and who were previously treated with any AAD (HR 0.70, 95% CI 0.59–0.82; \( P < 0.001 \)), even if the reason for discontinuation was lack of efficacy.72

**Comparative studies with other antiarrhythmic drugs**

There are limited head-to-head comparisons of dronedarone and other AADs. Although dronedarone was less effective at decreasing AF recurrence in the DIONYSSOS trial, dronedarone demonstrated a better safety profile and lower premature drug discontinuation vs. amiodarone (10.4% vs. 13.3%).4 The safety benefits with dronedarone vs. amiodarone were demonstrated despite the short follow-up of this study, which may have limited the number of AEs often seen with long-term use of amiodarone.4 A meta-analysis on the safety of amiodarone and dronedarone in RCTs found that dronedarone therapy was associated with fewer AEs and less discontinuation of treatment than amiodarone therapy, although the efficacy of dronedarone in maintaining SR was lower than amiodarone.20

In the EFFECT-AF study (actual drug use analysis), dronedarone had a similar effectiveness profile to the group of other AADs (Class I/A/C AADs, sotalol, and amiodarone) in confirmed AF recurrence rates (49.93/100 person-years and 53.83/100 person-years, respectively; \( P = 0.4269 \)). However, there were significantly lower rates of CV hospitalizations and HF in dronedarone- vs. other AAD-treated patients (24.72/100 person-years vs. 39.78/100 patient-years; \( P = 0.0001 \)).67

In a retrospective cohort study including 123 consecutive patients with paroxysmal or persistent AF treated with either dronedarone or flecainide, dronedarone treatment was as effective as flecainide in reducing AF recurrence, with an acceptable safety profile in comparison with flecainide (HR 0.68, 95% CI 0.18–2.53; \( P = 0.566 \)). There were AF recurrences in 36.6% of flecainide-treated patients vs. 21% in the dronedarone arm (\( P = 0.073 \)), despite more frequent prescription of dronedarone in patients with more baseline comorbidities, and after the failure of at least one previous AAD.73 A RCT comparing the effect of dronedarone and propafenone (\( N = 98 \)) in maintaining SR in patients with AF following electrical cardioversion found that the two drugs demonstrated similar efficacy. The median [range] ventricular rate at first recurrence of AF was numerically lower for dronedarone (76.5 [67.3–86.5] b.p.m.) vs. propafenone (83.0 [71.0–96.0] b.p.m.); however, the difference was not statistically significant (\( P = 0.059 \)).74

In summary, dronedarone has been shown to be effective in reducing AF burden and CV hospitalization rates in both placebo-controlled trials and real-world studies. When considered alongside its unique safety profile, with a lower risk of ventricular pro-arrhythmia compared with other AADs, these observations should be the principal reasons for choosing dronedarone for rhythm control. This could be particularly relevant in moderate-risk patients, such as those with hypertensive cardiomyopathy or ischaemic heart disease.

### Conclusion

Recent real-world studies coupled with post-market surveillance have provided evidence that dronedarone is a safe and effective drug for AF treatment. Several real-world studies have shown that the liver safety profile of dronedarone is similar to that of other AADs, while the risk of proarhythmic events is lower with dronedarone than with other agents. Data on the interaction between dronedarone and apixaban, and data on dronedarone and edoxaban in RCTs, suggest there are no significant safety risks for patients receiving these drugs, but there is less evidence to support the use of dronedarone with other DOACs. The concomitant use of digoxin with dronedarone may have been responsible for some of the negative effects of dronedarone in ANDROMEDA and PALLAS and should be avoided.

In addition, liver enzyme elevations seen in the AF population may be a result of comorbidities and polypharmacy rather than one specific drug. Although LFTs are recommended for dronedarone, as well as for other agents with reported alterations of hepatic enzymes (e.g., amiodarone), the more stringent EMA recommendations for dronedarone do not take into account recent real-world studies presented in this review.

### Table 5 The differing approaches between agencies on LFT policy for dronedarone

| Organization | Liver function testing policy for dronedarone | LFT before treatment | LFT after start of treatment |
|--------------|-----------------------------------------------|----------------------|-----------------------------|
| FDA          | No                                            | Consider obtaining periodic hepatic serum enzymes, especially during the first 6 months of treatment | After 1 week |
| EMA          | Yes                                           | • After 1 week  
• After 1 month of treatment initiation  
• Repeated monthly for first 6 months  
• At months 9 and 12  
• Periodically after first year |

EMA, European Medicines Agency; FDA, Food and Drug Administration; LFT, liver function test.
Supplementary material

Supplementary material is available at Europace online.

Acknowledgements

The authors thank Mattias Wieloch, MD, PhD from Sanofi for critical review and for providing the requested primary data on dronedarone liver safety (Table 4), as well as data from the post hoc analysis of the DIONYSOS trial (Figure 5). The authors also thank Dan Smalley, PhD and Niki Panagiotaki, PhD from HealthCare21 Communications Ltd, Macclesfield, Cheshire, SK10 2XA, UK for providing medical writing support. Responsibility for all opinions, conclusions, and interpretation of data lies with the authors.

Funding

This work was supported by funding from Sanofi in accordance with Good Publication Practice (GPP3) guidelines. No author was paid for services involved in writing this manuscript.

Conflict of interest

G.B.: speaker’s fees from Biotronik, Boehringer Ingelheim, Boston and Medtronic, and advisory board fees from Sanofi; C.B.L., G.L.B., A.C., I.F.L., A.J.C.: advisory board fees from Sanofi; S.H.H.: consultancy, advisory board or speaker’s fees from Abbott, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Boston Scientific, Cardiome, Forest RI, Gilead, Johnson & Johnson, Medtronic, Pfizer, Portola, Sanofi, Servier and Zoll; L.B.: advisory board fees from Sanofi and Bristol-Myers Squibb, honoraria from Bristol-Myers Squibb, Bayer and Pfizer, and speaker’s fees from Bayer; A.G.: research grants from the ‘Josel-Freitag-Stiftung’ and ‘Deutsche Herzstiftung e.V.’ speaker’s fees from AstraZeneca, Berlin Chemie, Boston Scientific, Boehringer Ingelheim, Bayer Health Care, BMS/Pfizer, Medtronic, Novartis, Sanofi, Daiichi-Sankyo and Omeics, and advisory board fees from Sanofi; C.W.I.: advisory board fees, honoraria from speaker’s bureau, reimbursement of travel/congress costs from Sanofi; J.L.M.: speaker’s fees, honoraria, consultancy fees, advisory board fees, investigator committee member fees from Cardiome, Abbott, Boston Scientific, Biotronik, Daiichi-Sankyo, Medtronic, Microport, Bayer, Biosense Webster, and Sanofi, and research grants from Microport, Boston Scientific, and Medtronic.

References

1. Hohnloser SH, Crijns HJ, Eickels M, van Gaudin C, Page RL, Torp-Pedersen C et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009;360:668–78.
2. Touboul P, Brugada J, Capucci A, Crijns H, Edvardsson N, Hohnloser SH. Dronedarone for prevention of atrial fibrillation: a dose-ranging study. Eur Heart J 2003;24:1481–7.
3. Singh BN, Connolly SJ, Crijns H, Roy D, Kowey PR, Capucci A et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med 2007;357:987–99.
4. Le Heuzey JY, De Ferrari GM, Radzki D, Santini M, Zhu J, Davy JM. A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: the DIONYSOS study. J Cardiovasc Electrophysiol 2010;21:597–605.
5. Ezekowitz MD, Ellendorf KB, DiMarco JP, Kasza K, Boddie A, Gебa GP et al. A placebo-controlled, double-blind, randomized, multicenter study to assess the effects of dronedarone 400 mg twice daily for 12 weeks on atrial fibrillation burden in subjects with persistent pacemakers. J Interv Card Electrophysiol 2015;42:69–76.
6. Reiffel JA, Connolly AJ, Belardinelli L, Zeng D, Karwatowska-Prokopczuk E, Olnsted A et al. The HARMONY trial: combined ranolazine and dronedarone in the management of paroxysmal atrial fibrillation: mechanistic and therapeutic synergism. Circ Arrhythm Electrophysiol 2015;8:1048–56.
7. Davy JM, Herold M, Hodgland C, Timmermans A, Alings A, Radzki D et al. Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the efficacy and safety of iLovedArone for the control of ventricular rate during atrial fibrillation (ERATO) study. Am Heart J 2008;156:527.e1–9.
8. Kober L, Torp-Pedersen C, McMurray JJV, Gotzsche O, Levy S, Crijns HJ et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008;359:2678–87.
9. Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Ameerova J et al. Dronedarone in high-risk permanent atrial fibrillation. N Engl J Med 2011;365:2266–76.
10. Hagens VE, Ranchor AV, Van Sonderen E, Bokker HA, Kamp O, Tijssen JGP et al. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the Rate Control Versus Electrical Cardioversion (RACE) study. J Am Coll Cardiol 2004;43:241–7.
11. Goette A, Benninger G, Pittrow D, Paar WD, Stritzky B, Vosch R. One-year surveillance and quality of life outcomes in patients with atrial fibrillation on dronedarone: prospective, non-interventional study in German ambulatory care. Herzschutz 2015;26:148–54.
12. Lin JL, Wu T-J, Chen C-P, Hsu J-C, Ueng K-C, Kuo J-Y et al. Observational study of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. JAMA 2019;321:1275.
13. Bloemström-Lundqvist C, Guszarson S, Schweizer J, Jensen SM, Bergfeldt L, Kneenback G et al. Effect of catheter ablation vs antiarrhythmic medication on quality of life in patients with atrial fibrillation: the CAPTAF randomized clinical trial. JAMA 2019;321:1059–68.
14. European Medicines Agency. Assessment report for Multaq. 2011. https://www.ema.europa.eu/documents/variation/report/multaq-h-c-1043-a20-05-epar-assess-report-variation_en.pdf (22 November 2018, date last accessed).
15. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016;18:1609–78.
16. Camm AJ, Lip GYH, De Caterina R, Savelieva I, Atar D, Hohnloser SH et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Europace 2012;14:1385–413.
17. Camm AJ, Kirchhof P, Lip GY, Schotten I, Savelieva I, Ernst S et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace 2010;12:3630–420.
18. January CT, Wann LS, Alpert JS, Calhoun H, Calkins H, Cleveland JC et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014;130:2071–104.
19. Piccini JP, Hasselblad V, Peterson ED, Washam JB, Caillf RM, Kong DF. Comparative efficacy of dronedarone and amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation. J Am Coll Cardiol 2009;54:1089–95.
20. Freemantle N, Lafuente-Lafuente C, Mitchell S, Eckert L, Reynolds M. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. Europace 2011;13:329–45.
21. Dages N, Varoucas C, Iliadomitsis EK, Lekakis JP, Ralliads LS, Anastassiou-Nana M. Dronedarone and the incidence of stroke in patients with paroxysmal or persistent atrial fibrillation: a systematic review and meta-analysis of randomized trials. Am J Cardiol Vascular Drugs 2011;11:395–400.
22. Chatterjee S, Ghosh J, Lichstein E, Aikat S, Mukherjee D. Meta-analysis of cardio-vascular outcomes with dronedarone in patients with atrial fibrillation or heart failure. Am J Cardiol 2012;110:607–13.
23. Hohnloser SH, Connolly SJ, John Camm A, Halperin JL, Radzki D. An individual patient-based meta-analysis of the effects of dronedarone in patients with atrial fibrillation. Europace 2014;16:1117–24.
24. Lafuente-Lafuente C, Valembois L, Bergmann J-F, Belmin J. Antiarrhythmics for maintaining sinus rhythm after cardioversion of atrial fibrillation. Cochrane Database Syst Rev 2015;CD005049.
25. Dienrberger I, Massaro G, Reggiani MLB, Lorenzetti S, Biffi M, Ziacchi M et al. Outcomes with dronedarone in atrial fibrillation: what differences between real-world practice and trials? A meta-analysis and meta-regression analysis. Curr Pharm Des 2017;23:944–51.
26. Frigbert L. Safety of dronedarone in routine clinical care. J Am Coll Cardiol 2014;63:3736–84.
27. Frigbert L. Safety of apixaban in combination with dronedarone in patients with atrial fibrillation. Int J Cardiol 2018;264:85–90.
28. Frigbert L. Ventricular arrhythmia and death among atrial fibrillation patients using anti-arrhythmic drugs. Am Heart 2018;205:118–27.
