REVIEW

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

Giuseppe Boriani[1], Carina Blomström-Lundqvist[2], Stefan H. Hohnloser[3],
Lennart Bergfeldt[4,5], Giovanni L. Botto[6], Alessandro Capucci[7],
Ignacio Fernández Lozano[8], Andreas Goette[9,10], Carsten W. Israel[3,11],
José L. Merino[12], and A. John Camm[13]*

[1]Division of Cardiology, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy; [2]Department of Medical Science and Cardiology, Uppsala University, Uppsala, Sweden; [3]Division of Clinical Electrophysiology, Department of Cardiology, J W Goethe University, Frankfurt, Germany; [4]Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [5]Västra Götaland, Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden; [6]ASST Rhodense, Ospedale di Circolo Rho, Milan, Italy; [7]Università Politecnica delle Marche, Ancona, Italy; [8]Sociedad Española de Cardiología, Madrid, Spain; [9]Medical Clinic II, Cardiology Department, St Vincenz-Krankenhaus Paderborn, Paderborn, Germany; [10]Working Group Molecular Electrophysiology, University Hospital Magdeburg, Magdeburg, Germany; [11]Clinic of Internal Medicine, Bethel-Clinic, Bielefeld, Germany; [12]Arrhythmia & Robotic EP Unit, Hospital Universitario La Paz-IdiPaz, Madrid, Spain; and [13]Cardiology Clinical Academic Group, Molecular and Clinical Sciences Institute, St George's University of London, Cranmer Terrace, London SW17 0RE, UK

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

---

endpoint of cardiovascular (CV) hospitalization or all-cause death in patients with paroxysmal or persistent AF [hazard ratio (HR) 0.76, 95% confidence interval (CI) 0.69–0.84; P < 0.001] vs. placebo (Table 1).[1]

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.[3] 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.[10] 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 ± 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.[11] 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 ± 15.1 (baseline) to 74.6 ± 11.5 (6 months) in an AF Effect on Quality of Life questionnaire.[12] 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.[13,14] 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.[14]

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[2]	270	Paroxysmal/persistent	Placebo	55% relative risk reduction in time to first AF recurrence
	ADONIS[3]	625	Paroxysmal/persistent	Placebo	26% reduction in the risk of adjudicated AF recurrence from day 5 to 12 months post-randomization
	EURIDIS[3]	612	Paroxysmal/persistent	Placebo	29% reduction in the risk of adjudicated AF recurrence from day 5 to 12 months post-randomization
	DIONYSOS[4]	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
	HESTIA[5]	112	Patients with permanent pacemakers	Placebo	54.4% reduction in AF burden
	HARMONY[6]	134	Paroxysmal with dual-chamber programmable pacemakers	Placebo	59% reduction in AF burden with combined treatment of dronedarone (225 mg bid) and ranolazine (750 mg bid)
Rate control-based	ERATO[7]	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[8]	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[1]	4628	Elderly patients with paroxysmal or persistent	Placebo	0.76 HR in all-cause mortality or CV hospitalization
	PALLAS[9]	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%).[15] 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).[25] 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).[29] 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.[33]

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.[31] 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

Table 2 Meta-analyses and recent real-world studies conducted on dronedarone

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
Recent real-world studies	**Registries used**	
Friberg[27]	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
Friberg[28]	Swedish patient register	Major bleeding was rare in patients with AF treated with apixaban in combination with dronedarone
Friberg[29]	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.

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
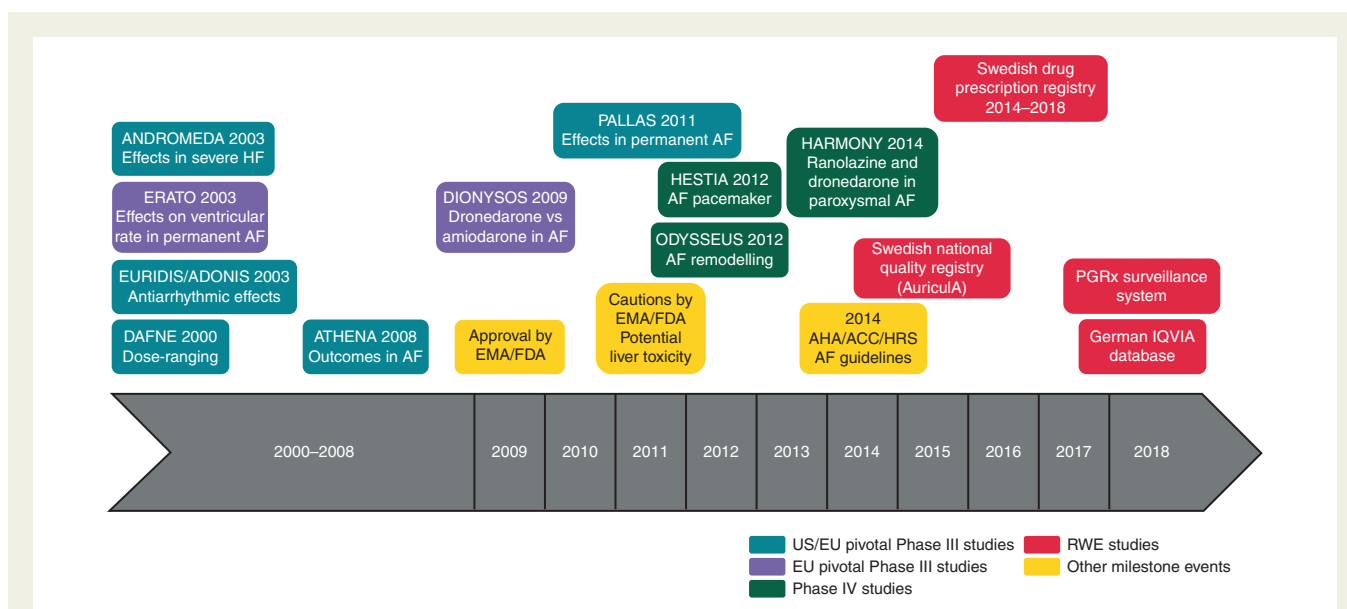
Figure 1 Timeline of key milestones for dronedarone. ACC, American College of Cardiology; AF, atrial fibrillation; AHA, American Heart Association; EMA, European Medicines Agency; FDA, Food and Drug Administration; HF, heart failure; HRS, heart rhythm society; RWE, real-world evidence.
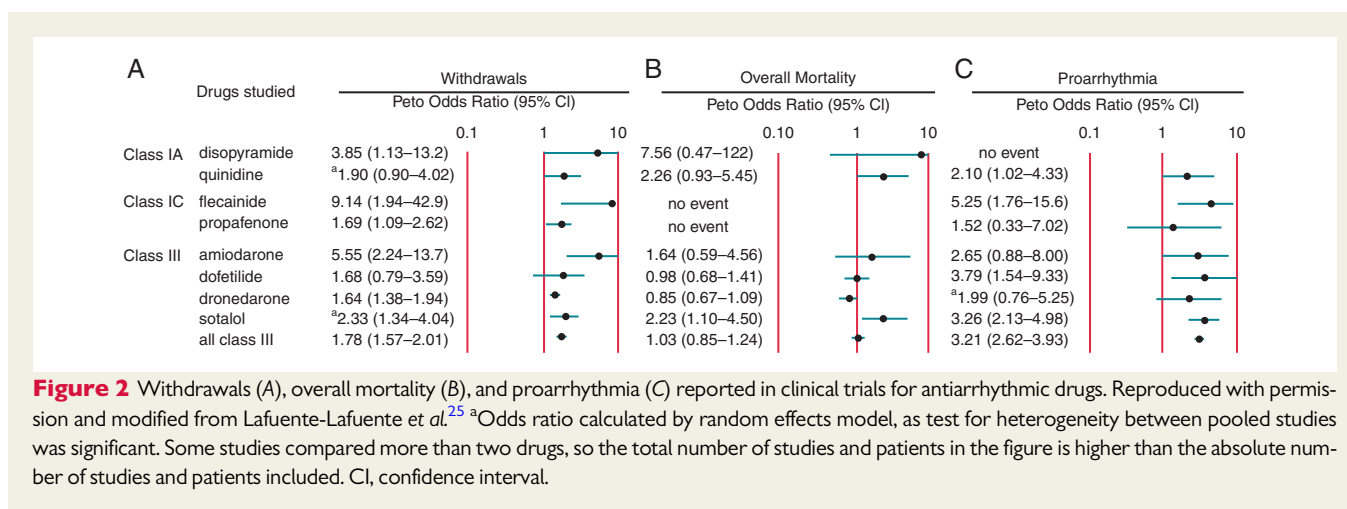
Figure 2 Withdrawals (*A*), overall mortality (*B*), and proarrhythmia (*C*) reported in clinical trials for antiarrhythmic drugs. Reproduced with permission and modified from Lafuente-Lafuente *et al.*[25] [a]Odds ratio calculated by random effects model, as test for heterogeneity between pooled studies 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.

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]

Other data on direct oral anticoagulants and dronedarone
In a retrospective cohort study on a Taiwanese population of 91 330 patients with non-valvular AF, no difference was found in the adjusted incidence rate ratio of major bleeding risk between concomitant use of dronedarone and dabigatran (0.89, 99% CI 0.54–1.45), apixaban (0.68, 99% CI 0.33–1.41), or rivaroxaban (0.92, 99% CI 0.68–1.24) vs. DOAC use alone. In contrast, amiodarone increased the risk of major bleeding when used concomitantly with dabigatran or rivaroxaban vs. DOAC use alone.[54]

　　Randomized controlled trials investigating concomitant use of dronedarone with DOACs are limited. This is particularly true for dabigatran and rivaroxaban, which have only been studied in combination
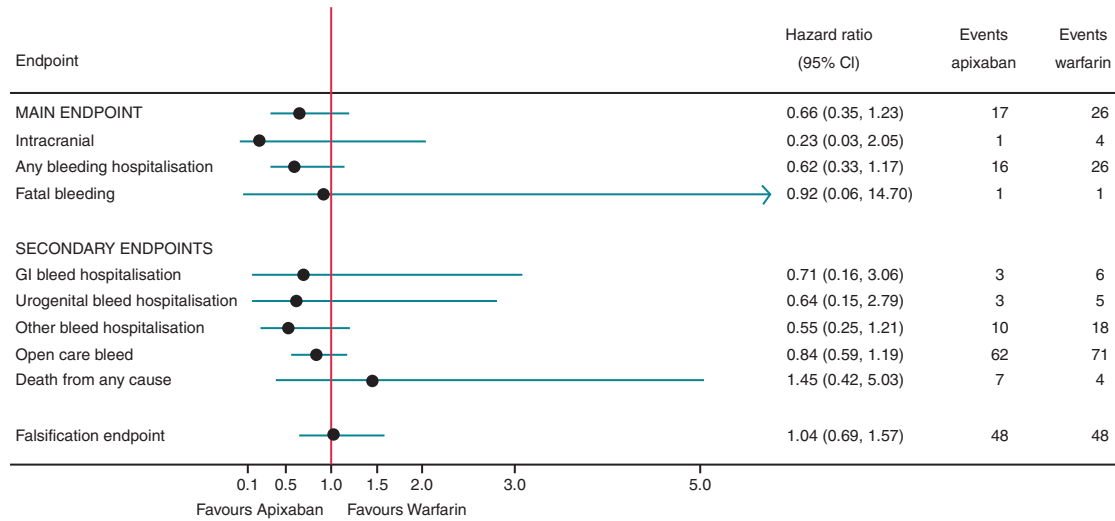
Figure 3 Hazard ratios for bleeding outcomes with apixaban–dronedarone and warfarin–dronedarone combinations. Reproduced with permission from Friberg.[28] CI, confidence interval; GI, gastrointestinal.

with dronedarone in a recent small study.[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.[28]

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.[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.[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.[56] International normalized ratio elevations have been reported in postmarketing cases in warfarin-treated patients initiated on dronedarone, and the EMA recommends monitoring INR levels following initiation with dronedarone when treated concomitantly with warfarin.[57]

Concomitant use of digoxin with dronedarone

Digoxin treatment itself may be associated with an increase in allcause mortality in patients with AF, as found in a retrospective analysis of the ROCKET-AF trial,[42] and when used for rate control in

patients with AF with or without HF in the AFFIRM study.[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; $P < 0.01$).[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; $P < 0.01$).[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 proarrhythmia, 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.[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; $P = 0.046$), 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; $P = 0.03$)], but a significant number of these patients were treated with digoxin concomitantly with dronedarone.[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.[45] Also, a study on experimental models comparing concomitant use of dronedarone and amiodarone with the digitalis glycoside ouabain in rabbits found that ouabain mediated a shortening of the ventricular refractory period, opposing the antiarrhythmic increases induced by dronedarone or amiodarone.[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

increased risk of proarrhythmia.[62] In line with these findings, a case report showed that the combination of amiodarone and digitalis resulted in torsades de pointes in a patient with tachycardiomyopathy and no coronary artery disease.[63]

Hence, PK/PD data and experimental animal data support that in combination with dronedarone, digitalis 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.[61]

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).[27] However, as mentioned previously, these real-world data should be interpreted with caution.[33]

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.[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.[64]

Recent experimental data suggest that amiodarone- and dronedarone-induced hepatotoxicity may occur through a similar mechanism, specifically the inhibition of mitochondrial fatty acid β-oxidation,[65] 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.[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) ≥5× 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; $P = 0.2970$).[30] 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[61]

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 $P = 0.02$)							
Overall	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 $P = 0.002$)							
Overall	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 × 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.
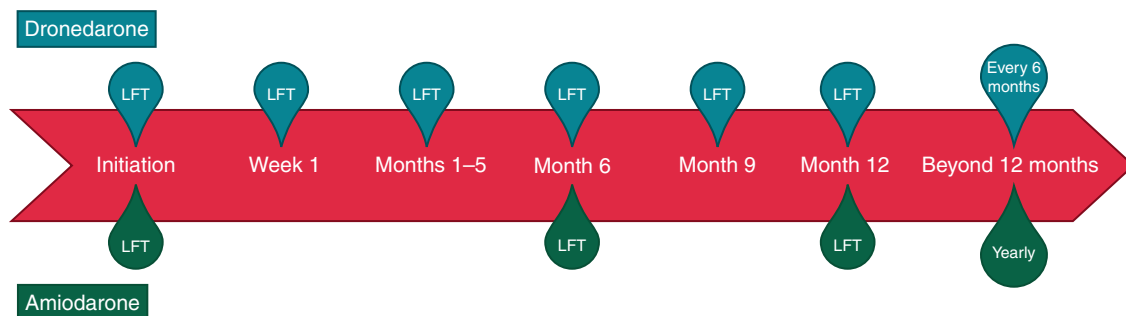
Figure 4 Differences in LFT regulations of EMA for amiodarone and dronedarone. EMA, European Medicines Agency; LFT, liver function test.

Table 4 Liver safety data from clinical trials with dronedarone

Number of patients with at least one post-baseline PCSA in liver parameters up to the last study drug intake +10 days during the on-treatment period[a]

| Parameter | PCSA criteria | Placebo | Dronedarone | | | Amiodarone |
		N = 564	400 mg bid N = 1238	600 mg bid N = 66	800 mg bid N = 62	600 mg/200 mg od N = 255
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 x ULN)[b]

| | Placebo | Dronedarone | | | Amiodarone |
	N = 2875	400 mg bid N = 3531	600 mg bid N = 66	800 mg bid N = 62	600 mg/200 mg od N = 255
TEAEs	74 (2.6%)	119 (3.4%)	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 (0.8%)
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[c]

| | Placebo | Dronedarone 400 mg bid |
	N = 2875	N = 3282
Number of events, n	74	97
Median survival (95% CI) (months)[d]	NC (NC to NC)	NC (NC to NC)
Cumulative incidence of events (95% CI)[d]		
6 months	0.013 (0.009–0.018)	0.020 (0.015–0.026)
1 year	0.022 (0.016–0.028)	0.030 (0.023–0.036)
2 years	0.040 (0.030–0.050)	0.039 (0.031–0.047)
Log-rank test P-value[e]	–	0.2566
Relative risk (95% CI)[f]	–	1.018 (0.749–1.385)

[a]All randomized and treated patients with AF/AFL excluding patients from the ATHENA trial.
[b]All randomized and treated patients in AF/AFL studies (DAFNE, EURIDIS, ADONIS, ATHENA, ERATO, and DIONYSOS).
[c]All randomized and treated patients with AF/AFL excluding patients from the DIONYSOS trial.
[d]Kaplan–Meier estimates.
[e]Log-rank test.
[f]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.
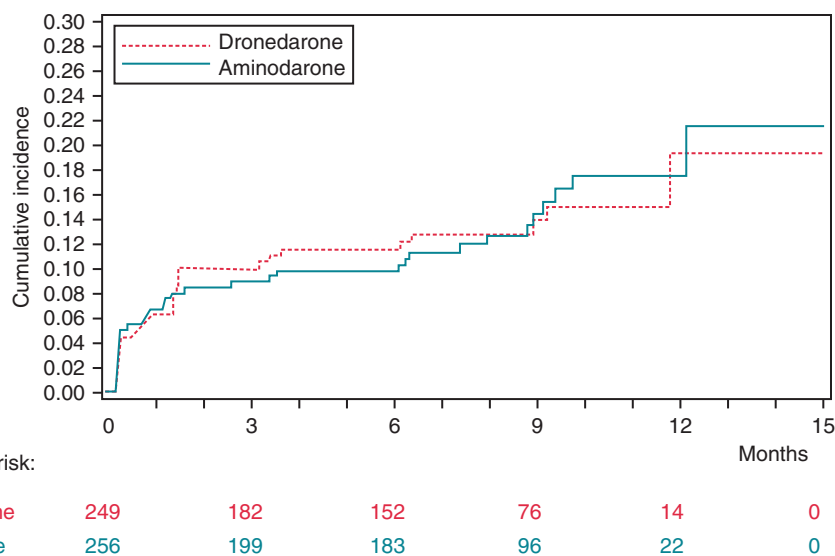
Figure 5 The Kaplan–Meier cumulative incidence curves from first study drug intake to first increase in liver enzymes (ALT and/or AST ≥2 × ULN and increase of >0.5 × ULN from baseline value) in DIONYSOS. ALT, alanine transaminase; AST, aspartate transaminase; ULN, upper limit of normal.

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

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
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.

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 DIONYSOS 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 IA/IC 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 proarrhythmic 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.

Supplementary material

Acknowledgements

Funding

References

1. Hohnloser SH, Crijns H, 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 J-Y, De Ferrari GM, Radzik D, Santini M, Zhu J, Davy J-M. 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, Ellenbogen KA, DiMarco JP, Kaszala K, Boddy A, Geba 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 permanent pacemakers. *J Interv Card Electrophysiol* 2015;**42**:69–76.
6. Reiffel JA, Camm AJ, Belardinelli L, Zeng D, Karwatowska-Prokopczuk E, Olmsted 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 J-M, Herold M, Hoglund C, Timmermans A, Alings A, Radzik D *et al.* Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the Efficacy and safety of dRonedArone for the cOntrol of ventricular rate during atrial fibrillation (ERATO) study. *Am Heart J* 2008;**156**:527.e1–9.
8. Køber L, Torp-Pedersen C, McMurray JJV, Gøtzsche O, Lévy S, Crijns H *et al.* Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008;**358**:2678–87.
9. Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J *et al.* Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med* 2011;**365**:2268–76.
10. Hagens VE, Ranchor AV, Van Sonderen E, Bosker 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. V, Bosch RF. One-year safety and quality of life outcomes in patients with atrial fibrillation on dronedarone: prospective, non-interventional study in German ambulatory care. *Herzschr Elektrophys* 2015;**26**:148–54.
12. Lin J-L, Wu T-J, Chen C-P, Hsu J-C, Ueng K-C, Kuo J-Y *et al.* Observational study of dronedarone in Taiwanese patients with atrial fibrillation. *J Formos Med Assoc* 2019. [EPub ahead of print].
13. Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH *et al.* Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;**321**:1275.
14. Blomström-Lundqvist C, Gizurarson S, Schwieler J, Jensen SM, Bergfeldt L, Kennebäck 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.
15. European Medicines Agency. Assessment report for Multaq. 2011. https://www.ema.europa.eu/documents/variation-report/multaq-h-c-1043-a20-05-epar-assessment-report-variation_en.pdf (22 November 2018, date last accessed).
16. 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.
17. 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.
18. Camm AJ, Kirchhof P, Lip GY, Schotten U, 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**:1360–420.
19. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, 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.
20. Piccini JP, Hasselblad V, Peterson ED, Washam JB, Califf 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.
21. 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.
22. Dagres N, Varounis C, Iliodromitis EK, Lekakis JP, Rallidis LS, Anastasiou-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 Cardiovasc Drugs* 2011;**11**:395–400.
23. Chatterjee S, Ghosh J, Lichstein E, Aikat S, Mukherjee D. Meta-analysis of cardiovascular outcomes with dronedarone in patients with atrial fibrillation or heart failure. *Am J Cardiol* 2012;**110**:607–13.
24. Hohnloser SH, Connolly SJ, John Camm A, Halperin JL, Radzik D. An individual patient-based meta-analysis of the effects of dronedarone in patients with atrial fibrillation. *Europace* 2014;**16**:1117–24.
25. 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.
26. Diemberger 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.
27. Friberg L. Safety of dronedarone in routine clinical care. *J Am Coll Cardiol* 2014;**63**:2376–84.
28. Friberg L. Safety of apixaban in combination with dronedarone in patients with atrial fibrillation. *Int J Cardiol* 2018;**264**:85–90.
29. Friberg L. Ventricular arrhythmia and death among atrial fibrillation patients using anti-arrhythmic drugs. *Am Heart J* 2018;**205**:118–27.

30. Grimaldi-Bensouda L, Wedemeyer H, Wiegand J, Lohse AW, Benichou J, Rossignol M et al. Dronedarone, amiodarone and other antiarrhythmic drugs, and acute liver injuries: a case-referent study. *Int J Cardiol* 2018;**266**:100–5.

31. Ehrlich JR, Look C, Kostev K, Israel CW, Goette A. Impact of dronedarone on the risk of myocardial infarction and stroke in atrial fibrillation patients followed in general practices in Germany. *Int J Cardiol* 2019;**278**:126–32.

32. Mochalina N, Juhlin T, Platonov PG, Svensson PJ, Wieloch M. Concomitant use of dronedarone with dabigatran in patients with atrial fibrillation in clinical practice. *Thromb Res* 2015;**135**:1070–4.

33. Reimold FR, Reynolds MR. Proarrhythmia and death with antiarrhythmic drugs for atrial fibrillation, and the unfulfilled promise of comparative effectiveness research. *Am Heart J* 2018;**205**:128–30.

34. Moro S, Ferreiro M, Celestino D, Medei E, Elizari MV, Sicouri S. In vitro effects of acute amiodarone and dronedarone on epicardial, endocardial, and M cells of the canine ventricle. *J Cardiovasc Pharmacol Ther* 2007;**12**:314–21.

35. Connolly SJ, Crijns H, Torp-Pedersen C, Eickels M. V, Gaudin C, Page RL et al. Analysis of stroke in ATHENA: a placebo-controlled, double-blind, parallel-arm trial to assess the efficacy of dronedarone 400 mg BID for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter. *Circulation* 2009;**120**:1174–80.

36. Pisters R, Hohnloser SH, Connolly SJ, Torp-Pedersen C, Naditch-Brûlé L, Page RL et al. Effect of dronedarone on clinical end points in patients with atrial fibrillation and coronary heart disease: insights from the ATHENA trial. *Europace* 2014;**16**:174–81.

37. Bukowska A, Hammwöhner M, Sixdorf A, Schild L, Wiswedel I, Röhl F-W et al. Dronedarone prevents microcirculatory abnormalities in the left ventricle during atrial tachypacing in pigs. *Br J Pharmacol* 2012;**166**:964–80.

38. Goette A, Bukowska A, Lillig CH, Lendeckel U. Oxidative stress and microcirculatory flow abnormalities in the ventricles during atrial fibrillation. *Front Physiol* 2012;**3**:236.

39. Skyschally A, Heusch G. Reduction of myocardial infarct size by dronedarone in pigs–a pleiotropic action? *Cardiovasc Drugs Ther* 2011;**25**:197–201.

40. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;**146**:857–67.

41. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;**369**:2093–104.

42. Washam JB, Stevens SR, Lokhnygina Y, Halperin JL, Breithardt G, Singer DE et al. Digoxin use in patients with atrial fibrillation and adverse cardiovascular outcomes: a retrospective analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). *Lancet* 2015;**385**:2363–70.

43. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–51.

44. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;**365**:981–92.

45. Wessler JD, Grip LT, Mendell J, Giugliano RP. The P-glycoprotein transport system and cardiovascular drugs. *J Am Coll Cardiol* 2013;**61**:2495–502.

46. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. *Europace* 2018;**20**:1231–42.

47. Wieloch M, Själander A, Frykman V, Rosenqvist M, Eriksson N, Svensson PJ. Anticoagulation control in Sweden: reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA. *Eur Heart J* 2011;**32**:2282–9.

48. Ehrlich JR. Re-gaining confidence in contemporary dronedarone use. *Int J Cardiol* 2018;**264**:97–8.

49. European Medicines Agency. *Variation assessment report for Multaq.* 2012. https://www.ema.europa.eu/documents/variation-report/multaq-h-c-1043-ii-20-epar-assessment-report-variation_en.pdf (26 November 2018, date last accessed).

50. European Medicines Agency. *Lixiana SmPC.* 2017. https://www.ema.europa.eu/documents/product-information/lixiana-epar-product-information_en.pdf (22 November 2018, date last accessed).

51. Salazar DE, Mendell J, Kastrissios H, Green M, Carrothers TJ, Song S et al. Modelling and simulation of edoxaban exposure and response relationships in patients with atrial fibrillation. *Thromb Haemost* 2012;**107**:925–36.

52. Mendell J, Zahir H, Matsushima N, Noveck R, Lee F, Chen S et al. Drug-drug interaction studies of cardiovascular drugs involving P-glycoprotein, an efflux

53. transporter, on the pharmacokinetics of edoxaban, an oral factor Xa inhibitor. *Am J Cardiovasc Drugs* 2013;**13**:331–42.

53. Escobar C, Arceluz M, Montes de Oca R, Mori R, López-Sendón JL, Merino JL. Concomitant rivaroxaban and dronedarone administration in patients with non-valvular atrial fibrillation. *Rev Esp Cardiol (Engl Ed)* 2017;**70**:121–2.

54. Chang S-H, Chou I-J, Yeh Y-H, Chiou M-J, Wen M-S, Kuo C-T et al. Association between use of non-vitamin K oral anticoagulants with and without concurrent medications and risk of major bleeding in nonvalvular atrial fibrillation. *JAMA* 2017;**318**:1250–9.

55. Shirolkar SC, Fiuzat M, Becker RC. Dronedarone and vitamin K antagonists: a review of drug-drug interactions. *Am Heart J* 2010;**160**:577–82.

56. Advisory committee meeting of the cardiovascular and renal drugs division of the US Food and Drug Administration. *Multaq briefing document.* 2009. https://wayback.archive-it.org/7993/20170405212856/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM176354.pdf (26 November 2018, date last accessed).

57. European Medicines Agency. *Multaq SmPC.* 2018. https://www.ema.europa.eu/documents/product-information/multaq-epar-product-information_en.pdf (22 November 2018, date last accessed).

58. Whitbeck MG, Charnigo RJ, Khairy P, Ziada K, Bailey AL, Zegarra MM et al. Increased mortality among patients taking digoxin—analysis from the AFFIRM study. *Eur Heart J* 2013;**34**:1481–8.

59. Vamos M, Erath JW, Hohnloser SH. Digoxin-associated mortality: a systematic review and meta-analysis of the literature. *Eur Heart J* 2015;**36**:1831–8.

60. Vamos M, Erath JW, Benz AP, Lopes RD, Hohnloser SH. Meta-analysis of effects of digoxin on survival in patients with atrial fibrillation or heart failure: an update. *Am J Cardiol* 2019;**123**:69–74.

61. Hohnloser SH, Halperin JL, Camm AJ, Gao P, Radzik D, Connolly SJ et al. Interaction between digoxin and dronedarone in the PALLAS trial. *Circ Arrhythm Electrophysiol* 2014;**7**:1019–25.

62. Frommeyer G, Puckhaber D, Ellermann C, Dechering DG, Kochhäuser S, Leitz P et al. Interactions of digitalis and class-III antiarrhythmic drugs: amiodarone versus dronedarone. *Int J Cardiol* 2017;**228**:74–9.

63. Guerra F, Brambatti M, Matassini MV, Capucci A. Amiodarone and digitalis: an odd couple in a tachycardiomyopathic patient. *Case Rep Intern Med* 2014;**1**:41.

64. European Medicines Agency. *European Medicines Agency recommends restricting use of Multaq.* 2011. https://www.ema.europa.eu/documents/press-release/european-medicines-agency-recommends-restricting-use-multaq_en.pdf (26 November 2018, date last accessed).

65. Felser A, Stoller A, Morand R, Schnell D, Donzelli M, Terracciano L et al. Hepatic toxicity of dronedarone in mice: role of mitochondrial β-oxidation. *Toxicology* 2014;**323**:1–9.

66. Felser A, Blum K, Lindinger PW, Bouitbir J, Krähenbühl S. Mechanisms of hepatocellular toxicity associated with dronedarone—a comparison to amiodarone. *Toxicol Sci* 2013;**131**:480–90.

67. Khachatryan A, Merino JL, Abajo FJ, Botto GL, Kirchhof P, Breithardt G et al. International multicentre cohort study on relative effectiveness of dronedarone and other antiarrhythmic drugs for atrial fibrillation in real world practice (EFFECT-AF). Poster presented at EHRA 2019, Lisbon, Portugal; 2019.

68. Tave A, Goehring E, Desai V, Wu C, Bohn R, Shara N. Adjudicating serious liver injury/disease and interstitial lung disease in electronic health records or claims data. *Pharmacoepidemiol Drug Saf* 2018;**27**:119.

69. Makar GA, Weiner MG, Kimmel SE, Bennett D, Burke A, Yang Y-X et al. Incidence and prevalence of abnormal liver associated enzymes in patients with atrial fibrillation in a routine clinical care population. *Pharmacoepidemiol Drug Saf* 2008;**17**:43–51.

70. Kim MH, Lin J, Jhaveri M, Koren A. Impact of dronedarone treatment on health-care resource utilization in patients with atrial fibrillation/flutter. *Adv Ther* 2014;**31**:318–32.

71. Goehring E, Bohn R, Pezzullo J C, Jones J, Deslandes B, Bozzi S et al. Real-life comparison of dronedarone with other antiarrhythmic drugs on cardiovascular outcomes in atrial fibrillation: an updated analysis of a large US population. *J Cardiovasc Electr* 2014;**25**:558.

72. Guerra F, Hohnloser SH, Kowey PR, Crijns H, Aliot EM, Radzik D et al. Efficacy and safety of dronedarone in patients previously treated with other antiarrhythmic agents. *Clin Cardiol* 2014;**37**:717–24.

73. Sánchez Soriano RM, Chamorro Fernández CI, Ruiz Nodar JM, Chamorro Fernández AJ, Grau Jornet G, Nuñez Villota J. Comparison of the efficacy and safety of dronedarone and flecainide as maintenance antiarrhythmic therapy for sinus rhythm in atrial fibrillation. *Arch Cardiol Mex* 2018;**88**:204–11.

74. Chun KJ, Byeon K, Im SI, Park K-M, Park S-J, Kim JS et al. Efficacy of dronedarone versus propafenone in the maintenance of sinus rhythm in patients with atrial fibrillation after electrical cardioversion. *Clin Ther* 2014;**36**:1169–75.