Dronedarone (Multaq®) for the treatment of atrial fibrillation

The prevalence of atrial fibrillation (AF) is increasing as well as the population is aging. Currently the therapeutic options for the maintenance of sinus rhythm are limited and many older antiarrhythmic drugs often have severe adverse effects causing discontinuation. Recent studies indicated that dronedarone, a multiple ion channel inhibitor, may be a safer but less effective alternative to amiodarone for the maintenance of sinus rhythm in paroxysmal AF and for reducing hospitalizations associated with AF. In this article, we aim to summarize available experimental and clinical trial-derived data over dronedarone’s efficacy, safety and indications, to express our opinion on its potential value for AF patients and to discuss its implementation to daily clinical practice for the management of AF.

**KEYWORDS:** atrial fibrillation  dronedarone  maintenance of sinus rhythm

Atrial fibrillation (AF) is a major public health problem and its complications lead to increased hospitalizations, mortality and healthcare costs [1,2]. Advanced age (>75 years), history of prior stroke or transient ischemic attack (TIA), presence of diabetes mellitus, hypertension, cardiac failure and vascular disease are all associated with nonvalvular AF patients and the risk of complications, such as stroke [3,4].

There is evidence indicating that rhythm and rate control strategies may have a similar impact on cardiovascular outcomes and life expectancy in AF patients. The results of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study indicated that management of AF with the rhythm-control strategy offers no survival advantage over the rate-control strategy; indeed, a rate-control strategy has potential advantages including decreased risk of adverse drug effects [5,6]. The lack of reliable antiarrhythmic drugs with proven efficacy, safety and tolerability is another reason for rate control strategy. Whilst amiodarone is still the most effective drug for the rhythm control strategy in AF patients [7], a safer (but probably less effective) alternative to amiodarone, dronedarone (Multaq®, Sanofi Aventis, Surrey, UK) has been developed and assessed in clinical trials. In this article we aim to discuss dronedarone’s advantages and disadvantages and its implementation to daily therapeutic practice in AF patients.

**Pharmacology**

Proarrhythmias and toxicity are the major problem of almost all antiarrhythmic drugs for rhythm control in AF patients. For example, class 1A antiarrhythmic drugs have been demonstrated to increase the risk for all-cause mortality by twofold when compared with placebo [8].

Currently, the most effective antiarrhythmic drug for rhythm control in AF patients is amiodarone, which has significant adverse effects that limit its administration.

In order to diminish side effects of amiodarone that are attributed to the iodine ring, dronedarone (SR 33589 or N,N-dibutyl-3-[4-((2-butyl-5-methylsulphonamido)benzofuran-3-yl-carbonyl)phenoxy]propylamine) has been developed by the removal of the iodine ring, addition of methyl sulfonamide and modification of the N-terminal region (Figure 1) [9]. The removal of the iodine ring aimed to diminish organ toxicity (e.g., liver, skin, thyroid gland) while the addition of the methyl sulfonamide group aimed to increase lipophilicity, which shortens the half-life of the drug and reduces tissue accumulation. Dronedarone has a great ability to block multiple ion channels over transmembrane potassium currents, L-type calcium and sodium currents, and also α- and β-adrenergic receptors. Dronedarone has a wide range of electrophysiological properties (e.g., prolongation of the action potential duration, inhibition of adrenoceptors, stronger inhibition of atrial sodium currents when compared to amiodarone, inhibition of the delayed rectifier potassium current [IKr] and L-type calcium currents) in recent studies [10–12].

The absorption of dronedarone is 70–94% once given orally and it can increase up to threefold in fed conditions. Dronedarone undergoes...
a first pass metabolism that diminishes the bioavailability to 15%. Steady state plasma concentrations are reached in a week by the administration of dronedarone 400 mg twice daily. The elimination half-life of dronedarone is approximately 30 h. Dronedarone is primarily metabolized by hepatic cytochrome P450 3A4 (CYP3A4) therefore interacts with other drugs using the CYP450 systems. Inhibitors and inducers of CYP3A4 may interact with dronedarone. Dronedarone is a moderate inhibitor of CYP3A4, a mild inhibitor of CYP2D6 and a potent inhibitor of P-glycoproteins and it may interact with medicinal product substrates of P-glycoproteins, CYP3A4 or CYP2D6. Dronedarone has no significant potential to inhibit other cytochromes including CYP1A2, CYP 2C9, CYP2C19, CYP2C8 and CYP2B6 [101,102].

Clinical evidence

The efficacy and safety of dronedarone has been recently assessed in various clinical trials (Table 1).

The Dronedarone Atrial Fibrillation Study after Electrical Cardioversion (DAFNE) was the Phase II prospective, placebo-controlled clinical trial designed to determine the most appropriate dose of dronedarone for the prevention of AF recurrence following cardioversion [13]. A total of 270 patients were randomized to one of three doses of dronedarone (800, 1200 or 1600 mg daily), 79 and 199 patients in whom sinus rhythm was restored pharmacologically or after cardioversion have entered the maintenance phase of the study for 6 months. Dronedarone provided dose-dependent spontaneous conversion to sinus rhythm in 5.8 to 14.8% patients (p = 0.026) when compared to 3.1% on placebo. The incidence of successful electrical cardioversion was not statistically different among groups: 77.3% (800 mg), 87.9% (1200 mg) and 76.6% (1600 mg), compared with 73% in the placebo group. The results of the DAFNE study indicated that dronedarone 800 mg daily (400 mg twice daily) significantly increased the average time to the first AF recurrence when compared to placebo (median time 60 vs 5.3 days in dronedarone and placebo groups respectively, relative risk reduction 55% [95% CI: 28–72%]). Of note, higher doses of dronedarone did not provide additional benefits. Side effects (most frequently, gastrointestinal side effects) were dose dependent. Drug-induced QT prolongation has been noticed in patients receiving 1600 mg daily, and has not been demonstrated in patients receiving 800 mg daily; there was no evidence for dronedarone-associated proarrhythmic reactions in any patient. At a dose of 800 mg daily the drug was well tolerated (the discontinuation rate due to adverse events was 3.9 vs 0% in the placebo group) and proved to be safe during short-term exposure [13].

The DAFNE study had premature drug discontinuations in 22.6 and 3.9% of subjects who received 1600 and 800 mg dronedarone, respectively. The major cause of drug discontinuation was reported to be gastrointestinal side effects [13]. Of note, there was no evidence of thyroid, eye or lung toxicity with dronedarone [13]. This was the reason to limit the dronedarone dose to 800 mg/day, and this dose of dronedarone has been used in Phase III clinical trials.

The European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the maintenance of Sinus Rhythm (EURIDIS) and the American–Australian–African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS) were identical, multi-center, double-blind, randomized trials, which have investigated the efficacy of dronedarone for maintaining sinus rhythm after electrical, pharmacologic, or spontaneous conversion from AF or atrial flutter [14]. All patients were in sinus rhythm for at least 1 h before randomization and none of the subjects had severe heart failure. Heart rhythm was monitored transtelephonically on days 2, 3 and 5; at months 3,
The composite primary end point (time to first AF recurrence or premature drug discontinuation) was 75.1% in the placebo group versus 69.3% in the dronedarone group (HR: 0.73; 95% CI: 0.59–0.92; p = 0.001). Furthermore, dronedarone significantly reduced the ventricular rate response (17.1% vs 24.3% in the placebo group; HR: 0.66; 95% CI: 0.47–0.93; p = 0.02). Analysis indicated that dronedarone significantly reduced the rate of occurrence of atrial fibrillation (32.8% vs 42.4% in the placebo group; HR: 0.78; 95% CI: 0.59–0.99; p = 0.047) [14].

Table 1. Summary of clinical trials of dronedarone.

<table>
<thead>
<tr>
<th>Study name</th>
<th>Patients</th>
<th>Study protocol</th>
<th>Follow-up</th>
<th>Efficacy end points</th>
<th>Safety end points</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DARNE</td>
<td>199 persistent AF patients</td>
<td>Dronedarone 400, 800 mg twice daily vs placebo</td>
<td>6 months</td>
<td>Time to AF relapse 60 days vs 5.3 days (dronedarone vs placebo) p = 0.001</td>
<td>PDD (22.6 and 3.9% in 1600 vs 800 mg dronedarone, respectively)</td>
<td>[15]</td>
</tr>
<tr>
<td>EURIDIS/ADONIS</td>
<td>1237 patients at sinus rhythm with a recent AF episode in the last 3 months</td>
<td>828 patients, 400 mg twice daily dronedarone; 409 patients placebo</td>
<td>12 months</td>
<td>Time to AF recurrence EURIDIS; placebo 41 days, dronedarone 96 days, ADONIS; placebo 59 days, dronedarone 158 days</td>
<td>No increase in pulmonary, thyroid and liver toxicity</td>
<td>[17]</td>
</tr>
<tr>
<td>ERATO</td>
<td>174 persistent AF patients in rate control strategy</td>
<td>400 mg twice daily dronedarone or placebo</td>
<td>6 months</td>
<td>Dronedarone decreased heart rate by 11.7 bpm on day 14 and the effect was sustained at 6 months</td>
<td>A 41% increase in serum digoxin concentration in dronedarone group</td>
<td>[19]</td>
</tr>
<tr>
<td>ANDROMEDA</td>
<td>627 heart failure patients</td>
<td>310 patients, 400 mg twice daily dronedarone, 317 patients placebo</td>
<td>2 months</td>
<td>53 events in the dronedarone group (17.1%) and 40 events in the placebo group (12.6%; HR: 1.38, 95% CI: 0.92–2.09; p = 0.12)</td>
<td>In 2 months 25 patients in the dronedarone group (8.1%) and 12 patients in the placebo group (3.8%) died because of worsening heart failure (HR: 2.13; 95% CI: 1.07–4.25; p = 0.03)</td>
<td>[23]</td>
</tr>
<tr>
<td>ATHENA</td>
<td>4628 AF patients with additional risk factors for death</td>
<td>2301 patients, 400 mg twice daily dronedarone, 2327 patients placebo</td>
<td>21 ± 5 months</td>
<td>Hospitalization due to CV events or death from any cause 24% RRR, (HR: 0.76; 95% CI: 0.68–0.84; p &lt; 0.001)</td>
<td>PDD 696 (0.02%) in dronedarone, 716 (30.8%) in placebo</td>
<td>[21]</td>
</tr>
<tr>
<td>DIONYSOS</td>
<td>504 persistent AF patients</td>
<td>249 patients 400 mg twice daily dronedarone, 254 patients 600 mg q.d. 28 days then 200 mg q.d. amiodarone</td>
<td>7 months</td>
<td>AF recurrence or PDD 75.1% with dronedarone and 58.8% with amiodarone at 12 months (HR: 1.59; 95% CI: 1.28–1.98; p &lt; 0.0001)</td>
<td>PDD; dronedarone vs amiodarone (10.4 vs 13.3%) MSE 39.3 versus 44.5% (dronedarone vs amiodarone) at 12 months (HR: 0.80; 95% CI: 0.60–1.07; p = 0.129)</td>
<td>[16]</td>
</tr>
</tbody>
</table>

MSE was occurrence of thyroid, hepatic, pulmonary, neurologic, skin, eye or GI-specific events, or premature study drug discontinuation following an adverse event. AF: Atrial fibrillation; bpm: Beats per minutes; CI: Confidence interval; CV: Cardiovascular; GI: Gastrointestinal; HR: Heart rate; MSE: Main safety end point; PDD: Premature drug discontinuation; RRR: Relative risk reduction.
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The Efficacy and Safety of Dronedarone for Control of Ventricular Rate (ERATO) study assessed the efficacy of dronedarone for the control of ventricular rate in patients with permanent AF, when added to standard therapy [16]. The study enrolled 174 patients (85 to the dronedarone group, 400 mg twice daily and 89 to the placebo group) with AF of more than 6 months of duration and resting ventricular rate of at least ≥80 bpm. Overall, the vast majority of patients were older than 65 years, 49% of patients had hypertension, 39% had structural heart disease, 40% of patients had class I or II New York Heart Association (NYHA) heart failure. Added to standard rate control agents (β-blockers in 52% of patients), dronedarone significantly decreased mean 24 h ventricular rate (by 11.7 beats per min on day 14) and provided a mean reduction of 24.5 bpm in ventricular rate during maximal exercise compared to placebo (p < 0.0001), without any reduction in exercise tolerance as measured by maximal exercise duration. The effect of dronedarone on heart rate was sustained throughout the 6-month trial. In this short-term study dronedarone was well tolerated (permanent discontinuation for any treatment-emergent adverse events was 15% in the dronedarone group vs 10% in the placebo group), with no evidence of organ toxicities or proarrhythmias [16].

The ATHENA trial (A placebo-controlled, double-blind, parallel-arm trial to assess the efficacy of dronedarone 400mg twice daily for the prevention of cardiovascular hospitalization or death from any cause in patients with Atrial fibrillation/atrial flutter) investigated effects of dronedarone on mortality and morbidity among AF patients. In the ATHENA study, the primary outcome comprised the first hospitalization due to cardiovascular events or death [18]. The ATHENA study included 4628 patients (n = 2301 randomized to dronedarone and n = 2327 to placebo) with paroxysmal or persistent AF or flutter and at least one additional risk factor for cardiovascular events, including age greater than 75 years or aged 70 years with one or more of the following: hypertension, diabetes, prior stroke, TIA or systemic thromboembolism, left atrial enlargement (≥50 mm) or depressed left ventricle ejection fraction (≤40%) [18,19]. In the follow-up period (mean 21 ± 5 months) the primary outcome has been determined in 734 (31.9%) patients on dronedarone and 917 patients (39.4%) in the placebo group, with HR for dronedarone of 0.76 (95% CI: 0.69–0.84; p < 0.001). Dronedarone reduced the rate of hospitalization due to cardiovascular events (657 patients [29.3%] vs 859 patients [36.9%] in the placebo group; HR: 0.74; 95% CI: 0.67–0.82; p < 0.001), mainly by a reduction in the number of hospitalizations for AF, whereas there were no significant differences in the number of hospitalizations for heart failure or ventricular arrhythmia. First hospitalization for ventricular arrhythmia or nonfatal cardiac arrest was 13 (0.6%) in the dronedarone group and 12 (0.5%) in the placebo group, HR for dronedarone 1.09 (95% CI: 0.50–2–0.39), p = 0.83. A significant reduction in death from any cause was not demonstrated; however, there were significantly fewer deaths from cardiovascular causes in the dronedarone group than in the placebo group: 63 patients (2.7%) and 90 patients (3.9%) respectively (HR: 0.71; 95% CI: 0.51–0.98; p = 0.03). The rate of death from cardiac arrhythmia was also significantly reduced with dronedarone (HR: 0.55; 95% CI: 0.30–0.95).
A post-hoc analysis of ATHENA evaluated the relationship between clinical outcomes and dronedarone therapy in patients with stable heart failure (209 patients with NYHA class II/III heart failure and a left ventricle ejection fraction ≤40% at baseline) did not show an increase in mortality in the dronedarone group and demonstrated a reduction of cardiovascular hospitalization or death similar to overall study population [22]. However, in light of the ANDROMEDA study dronedarone should be contraindicated in patients with NYHA class IV or unstable NYHA classes II and III heart failure.

Place in therapy

- Patient selection

Currently, the US FDA has approved dronedarone for reducing the risk of cardiovascular hospitalization in patients with paroxysmal or persistent AF or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors (age >70 years hypertension, diabetes, prior cerebrovascular accident, left atrial diameter of at least 50 mm or left ventricular ejection fraction <40%), who are in sinus rhythm or who will be cardioverted [103]. Dronedarone has also been approved in the EU and is indicated in adult clinically stable patients with a history of, or current nonpermanent AF to prevent recurrence of AF or to lower ventricular rate [104–106].

Although dronedarone is less efficacious than amiodarone in the prevention of recurrent AF, it reduces the risk of cardiovascular hospitalization or death and appears to be a safer and well-tolerated drug than amiodarone in patients without decompensated heart failure. The latest appraisal of the NICE in the UK recommends the administration of dronedarone as a second-line treatment option for nonpermanent AF only in people whose AF is not controlled by first-line therapeutics (including β-blockers), and who have at least one of the following cardiovascular risk factors: hypertension requiring drugs of at least two different classes, diabetes mellitus, previous transient ischemic attack, stroke or systemic embolism, left atrial diameter of 50 mm or greater, left ventricular ejection fraction less than 40% or aged 70 years or older, and who do not have unstable NYHA class III or IV heart failure [23]. NICE also recommends that people who do not meet these criteria and are currently receiving dronedarone should have the option to continue treatment until they and their clinicians consider it appropriate to stop [23]. Due to

The effect of dronedarone remained consistent when all outcome events (hospitalization due to any cardiovascular event or death from any cause) during the study period were considered (1253 patients [54.5%] had an event in the dronedarone group compared to 1668 [71.7%] patients in the placebo group; HR: 0.76; 95% CI: 0.68–0.84; p < 0.001) [29].

In addition, a post-hoc analysis of the ATHENA trial has demonstrated that dronedarone reduced the risk of stroke from 1.8% per year to 1.2% per year (HR: 0.66; 95% CI: 0.46–0.96; p = 0.027). The effect of dronedarone was independent on underlying antithrombotic therapy, and it was significantly greater in patients with higher CHADS2 scores [20].

A multicenter double-blind randomized study, antiarrhythmic trial with dronedarone in Moderate to severe CHF evaluating morbidity (ANDROMEDA) aimed to assess the efficacy of dronedarone on hospitalization for heart failure and on mortality in patients hospitalized with new or worsening NYHA functional class III or IV heart failure with a wall motion index less than or equal to 1.2 (approximating an index <1.2). The study was designed to recruit 1000 patients, but after inclusion of 627 patients (310 in the dronedarone group and 317 in the placebo group), the trial was prematurely terminated (median follow-up of 2 months) for safety reasons as 25 of the patients randomized to dronedarone died, whereas only 12 patients randomized to placebo did (HR: 2.13; 95% CI: 1.07–4.25; p = 0.03). The excess mortality was predominantly related to worsening of heart failure. The risk of death associated with dronedarone was increased among patients with lower wall-motion index (WMI <1) compared with those who had higher wall-motion index (WMI ≥1). Incidence of death among patients with lower WMI in the dronedarone group was 15 out of 144 whereas it was reported to be four out of 180 in the placebo group, HR for death in the dronedarone group was noted 4.61 (95% CI: 1.531–3.9), p-value for interaction with WMI and incidence of death was 0.04. The primary end point did not differ significantly between the two groups: 53 events (17.1%) in the dronedarone group and 40 (12.6%) events in the placebo group (HR: 1.38; 95% CI: 0.92–2.09; p = 0.12). There was no difference in deaths after an additional 6 months without study treatment: 42 patients in the dronedarone group (13.5%) and 39 patients in the placebo group (12.3%) had died (HR: 1.13; 95% CI: 0.73–1.74; p = 0.6) [21].

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to the results of the ANDROMEDA study and lacking experience in stable heart failure patients with recent (1–3 months) NYHA class III heart failure or with left ventricular ejection fraction less than 35%, the use of dronedarone in unstable patients with NYHA class III and IV heart failure is not recommended [102].

The new European Society of Cardiology guidelines for the management of AF recommend dronedarone alongside with flecainide, propafenone and sotalol as a first-line treatment for the rhythm control in AF patients. Without significant structural heart disease (class I, level of evidence A) [4]. The guidelines suggest that dronedarone may also be preferable as the first therapeutic option for rhythm control in symptomatic AF patients with underlying cardiovascular disease (e.g., hypertrophy, ischemia and congestive heart failure) in view of its better safety and potential outcome benefit, with amiodarone as a second-line choice, should dronedarone fail to control symptoms [4]. Since dronedarone is contraindicated in patients with NYHA class III–IV or recently decompensated heart failure, amiodarone is the drug of choice in these patients. There is no evidence supporting routine administration of dronedarone in asymptomatic AF patients [4].

## Dosing & administration

Dronedarone therapy can be initiated in an outpatient setting. The recommended dosage of dronedarone is 400 mg twice daily with meals. If a dose is missed, patients are advised to take the next dose at the regular scheduled time and should not double the dose. Treatment with class I or III antiarrhythmics must be stopped before starting dronedarone [102]. The most significant drug interactions of dronedarone are listed in Table 2.

### Tolerability & adverse events

The most frequently observed adverse events in patients receiving dronedarone are elevated blood creatinine levels and prolongation of the QT interval. However, the increase in creatinine level may not reflect a deterioration in renal function. Dronedarone reduces renal creatinine clearance by approximately 18%, without evidence of an effect on the glomerular filtration rate, apparently as a result of a specific partial inhibition of tubular organic-cation transport of creatinine [24]. Dronedarone is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min) [102]. Although dronedarone prolongs the QT interval, the risk of torsades de pointes is low, which allows initiation of the drug in outpatients. There was one case of torsades de pointes in the ATHENA trial [19]. However, the risk of proarrhythmia could significantly increase in the setting of a QTc interval greater than 500 ms. Patients with a prolonged QTc were excluded from the drug trials, and baseline prolonged QTc interval (>500 ms) is a contraindication for dronedarone use [102]. Other common adverse events include bradycardia, gastrointestinal events, such as diarrhea and vomiting, rashes, pruritus, fatigue and asthenia. In the dose determination study (DAFNE), premature drug discontinuation mainly associated with

<table>
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<th>Interaction mechanism(s)</th>
<th>Consequences</th>
<th>Recommendation</th>
<th>Drug</th>
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<tr>
<td>CYP3A</td>
<td>Increased dronedarone exposure</td>
<td>Concomitant use is contraindicated</td>
<td>Macrolide antibiotics</td>
</tr>
<tr>
<td>CYP3A</td>
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<td>Antifungals</td>
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<tr>
<td>CYP3A</td>
<td>Increased dronedarone exposure</td>
<td>Concomitant use is contraindicated</td>
<td>Protease inhibitors</td>
</tr>
<tr>
<td>CYP3A</td>
<td>Fourfold increased simvastatin levels and risk of myopathy</td>
<td>Concomitant use with caution</td>
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<tr>
<td>CYP2D6 and p-glycoprotein</td>
<td>Increased β-blocker exposure</td>
<td>Concomitant use with caution</td>
<td>β-blockers</td>
</tr>
<tr>
<td>None</td>
<td>No substantial interaction and increase in INR</td>
<td>Close INR control</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Inhibition of p-glycoprotein transporter</td>
<td>2.5-fold increased digoxin exposure</td>
<td>Use half dose digoxin and monitor serum digoxin levels</td>
<td>Digoxin</td>
</tr>
<tr>
<td>CYP3A</td>
<td>1.4- to 1.7-fold increased exposure to CCBs</td>
<td>Concomitant use with caution</td>
<td>CCBs</td>
</tr>
<tr>
<td>Other</td>
<td>Prolonged QTc interval, torsades de pointes</td>
<td>Concomitant use is contraindicated</td>
<td>Tricyclic antidepressants</td>
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<tr>
<td>Other</td>
<td>Prolonged QTc interval, torsades de pointes</td>
<td>Concomitant use is contraindicated</td>
<td>Class I or III antiarrhythmics</td>
</tr>
</tbody>
</table>

CCB: Calcium channel blocker; INR: International normalized ratio.

Data taken from [13].
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Failure, or class II–III heart failure with a recent ventilation test abnormalities and hepatocellular injury fraction less than 35% as contraindications to decompensation and left ventricular ejection function were not significantly increased with dronedarone when compared to placebo. There was no significant difference in the number of serious treatment-emergent adverse events between the groups (19.9% in the dronedarone group and 21.1% in the placebo group) [19]. In the ANDROMEDA study dronedarone caused an increased mortality among heart failure patients that was mainly associated with worsening of heart failure [21]. The patient profile of the ANDROMEDA trial has become a ground for considering NYHA class IV heart failure, or class II–III heart failure with a recent decompensation and left ventricular ejection fraction less than 35% as contraindications to dronedarone use.

Of note, the US FDA recently issued a safety communication concerning possible liver function test abnormalities and hepatocellular injury in patients treated with dronedarone [100]. The FDA received several case reports of hepatocellular liver injury and hepatic failure in patients treated with dronedarone, including two postmarketing reports of acute hepatic failure requiring transplantation (both patients were female, hepatic injury occurred at 4.5 and 6 months after initiation of dronedarone) in patients with previously normal hepatic serum enzymes. In both cases, the explanted liver specimens showed evidence of extensive hepatocellular necrosis. In both cases, the explanted liver specimens showed evidence of extensive hepatocellular necrosis. Currently, periodic liver function tests are recommended in patients taking dronedarone, especially in the first 6 months of treatment [101]. More data from postmarketing studies will elucidate the real safety profile of dronedarone.

The PALLAS study, which was a placebo-controlled study on permanent AF patients aimed to assess dronedarone’s efficacy and safety in patients over 65 years of age with permanent AF; however, the study was stopped after enrollment of 3149 patients because of an increased rate of major cardiovascular events (stroke or myocardial infarction) or hospitalizations due to cardiovascular events, or death [102,103].

Conclusion

Dronedarone is a relatively new pharmacological option for the antiarrhythmic treatment of AF patients that can be used to maintain sinus rhythm and control ventricular rate during the relapsing atrial arrhythmias. The main purpose of its development was to reduce amiodarone’s many side effects with acceptable efficacy. Dronedarone is an antiarrhythmic drug that has been shown to reduce cardiovascular mortality or hospitalizations in AF patients. Current evidence supports the use of dronedarone with the purpose of reducing the risk of cardiovascular hospitalization in patients with paroxysmal or persistent AF or AFL, with a recent episode of AF/AFL and associated cardiovascular risk factors (aged >70 years, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter of at least 50 mm or left ventricular ejection fraction <40%), who are in sinus rhythm or who will be cardioverted. Dronedarone is contraindicated in unstable heart failure and liver failure patients. Current findings indicate that it may cause harm in permanent AF patients by increasing cardiovascular events. New studies with longer follow-up periods are required to elucidate the real-life safety (i.e., severe hepatotoxicity, increased stroke, myocardial infarction, hospitalizations or death), efficacy and tolerability of dronedarone in long-term therapy.
Financial & competing interests disclosure

N Kuzniatsova and B Pamukcu are funded by the European Society of Cardiology ‘Atherothrombosis Research Fellowships’. GYH Lip has received funding for research, educational symposia, consultancy and lecturing from different manufacturers of drugs used for the treatment of atrial fibrillation, including Sanofi Aventis, who market dronedarone. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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Dronedarone (Multaq®) for the treatment of atrial fibrillation