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

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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 [I_{Kr}] 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

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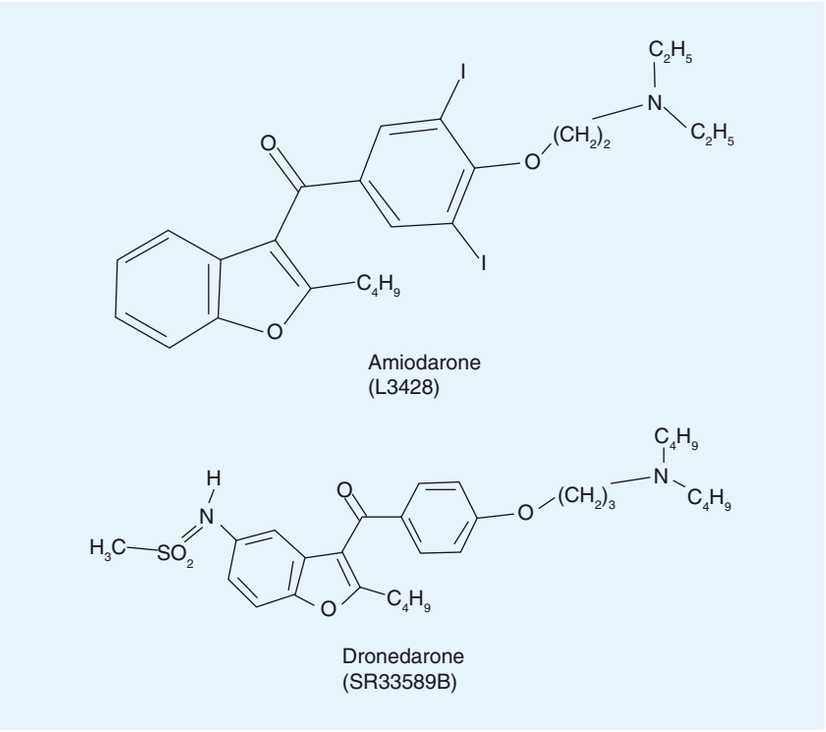

Figure 1. Amiodarone and dronedaorne.

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, multicenter, 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,

5, 7 and 10; and whenever patients had symptoms; and electrocardiography was performed at nine scheduled visits during a 12-month period. EURIDIS randomized 411 patients to dronedarone and 201 patients to placebo, whilst ADONIS randomized 417 patients to dronedarone and 208 patients to placebo. The median time to recurrence of AF in the European trial was 96 days in the dronedarone group versus 41 days in the placebo group. The corresponding durations in the American–Australian–African trial were 158 and 59 days. At 12 months, in the European trial 67.1% of dronedarone-treated patients had a recurrence of atrial arrhythmia compared with 77.5% of patients in the placebo group (hazard ratio [HR] for the dronedarone group, 0.78; 95% CI: 0.64–0.96; p = 0.01). In the American–Australian–African trial corresponding rates of atrial arrhythmia recurrence in dronedarone and placebo groups were 61.1 and 72.8%, respectively (HR: 0.73; 95% CI: 0.59–0.89, p = 0.002). Furthermore, dronedarone significantly reduced the ventricular rate response when compared to placebo during the recurrence of arrhythmia in both European and non-European trials (102.3 ± 24.7 vs 117.5 ± 29.1 and 104.6 ± 27.1 vs 116.6 ± 31.9 in EURIDIS and ADONIS, respectively). Interestingly, a post hoc analysis indicated that dronedarone significantly reduced the rate of hospitalization or death, only in the European trial (32 vs 21.2%; HR: 0.66; 95% CI: 0.47–0.93; p = 0.02) [14].

The DIONYSOS study (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) aimed to directly compare the efficacy and safety of dronedarone to amiodarone in patients with persistent AF [15]. The efficacy and safety of amiodarone (600 mg daily for 28 days, and 200 mg thereafter) and dronedarone (400 mg twice daily) were compared for at least 6 months in patients with persistent AF [16]. A total of 504 amiodarone naive AF patients were randomized to receive either dronedarone (n = 249) or amiodarone (n = 255). Median treatment duration was 7 months. The incidence of the composite primary end point (time to first AF recurrence or premature drug discontinuation for intolerance or lack of efficacy) was 75.1 and 58.8% in the dronedarone and amiodarone groups respectively, at the 12th month of treatment (HR: 1.59; 95% CI: 1.28–1.98; p < 0.001). The composite primary end point was mainly driven by the AF recurrence (including absence of conversion): 158 patients (63.5%) in the

Table 1. Summary of clinical trials of dronedarone.

Study name	Patients	Study protocol	Follow-up	Efficacy end points	Safety end points	Ref.
DAFNE	199 persistent AF patients	Dronedarone 400, 800 mg twice daily vs placebo	6 months	Time to AF relapse 60 days vs 5.3 days (dronedarone vs placebo) p = 0.001	PDD (22.6 and 3.9% in 1600 vs 800 mg dronedarone, respectively)	[15]
EURIDIS/ ADONIS	1237 patients at sinus rhythm with a recent AF episode in the last 3 months	828 patients, 400 mg twice daily dronedarone; 409 patients placebo	12 months	Time to AF recurrence EURIDIS; placebo 41 days, dronedarone 96 days, ADONIS; placebo 59 days, dronedarone 158 days	No increase in pulmonary, thyroid and liver toxicity	[17]
ERATO	174 persistent AF patients in rate control strategy	400 mg twice daily dronedarone or placebo	6 months	Dronedarone decreased heart rate by 11.7 bpm on day 14 and the effect was sustained at 6 months	A 41% increase in serum digoxin concentration in dronedarone group	[19]
ANDROMEDA	627 heart failure patients	310 patients, 400 mg twice daily dronedarone, 317 patients placebo	2 months	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)	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)	[23]
ATHENA	4628 AF patients with additional risk factors for death	2301 patients, 400 mg twice daily dronedarone, 2327 patients placebo	21 ± 5 months	Hospitalization due to CV events or death from any cause 24% RRR, (HR: 0.76; 95% CI: 0.68–0.84; p < 0.001)	PDD 696 (30.2%) in dronedarone, 716 (30.8%) in placebo Significantly higher GI events, bradycardia, QT prolongation and serum creatinine increase in dronedarone group	[21]
DIONYSOS	504 persistent AF	249 patients 400 mg twice daily dronedarone, 254 patients 600 mg q.d. 28 days then 200 mg q.d. amiodarone	7 months	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 < 0.0001)	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)	[16]

†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.

dronedarone group versus 107 patients (42%) in the amiodarone group, while the premature drug discontinuation was less frequent in the dronedarone group (10.4 compared with 13.3% in the amiodarone group). The rate of AF recurrence after conversion to sinus rhythm was 36.5 and 24.3% of patients in the dronedarone and amiodarone group, respectively. Adverse event rates were high for both drugs (39.3% with dronedarone vs 44.5% with amiodarone; HR: 0.80; 95% CI: 0.60–1.07; p = 0.13). However, the incidence of thyroid, neurological, skin and eye events was less with dronedarone compared to amiodarone. There was a trend toward less premature drug discontinuation due to adverse events in the dronedarone group (HR: 0.76; 95% CI: 0.48 to 1.19; p = 0.227) [15]. The results of the DIONYSOS study indicated that although amiodarone was more efficient for prolongation the time to first AF recurrence, drug discontinuation due to intolerance was more common. The DIONYSOS study provided limited information on the safety and efficacy of dronedarone since the follow-up period was far too short to evaluate long-term benefits and risks. On the other hand a superior efficacy in favor of amiodarone has been established in recent trials when indirectly compared to other antiarrhythmics, including sotalol and propafenone [17]. For now, we have safety data for a relatively short period of time for dronedarone. More data on the safety profile of dronedarone will be available in the near future after obtaining longer follow-up results since some of the organ toxicity may appear on longer treatment periods.

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: 0.502–0.39), 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:

0.34–0.88; p = 0.01). 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) [19].

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, antiarrhytnmic trial with dronedarone in Moderate to severe CHF evaluating morbidity decrease (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 ejection fraction of no more than 35%) [21]. 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].

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 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 2. Drugs that interact with dronedarone and interaction mechanisms.

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

CCB: Calcium channel blocker; INR: International normalized ratio.
Data taken from [13].

gastrointestinal side effects has been reported in 3.9% of patients receiving 800 mg dronedarone daily versus 0% in the placebo group [13]. No increased thyroid, eye or pulmonary toxicity of dronedarone has been reported.

The safety of dronedarone has also been evaluated in the EURIDIS and ADONIS trials (n = 1237, 12-month follow-up) [14]. Adverse events were similar between the study groups, and adverse events related study discontinuation rates have been 9.5% in the dronedarone and 6.1% in the placebo groups. Dronedarone has shown to reduce heart rate by 6.8%, prolonged QT interval by 23.4 ms, and QTc interval by 9.0 msec ($p < 0.001$ for all comparisons with the placebo group), without significant effects on the QRS duration. No increased proarrhythmia, pulmonary toxicity and neurological events have been reported in the EURIDIS-ADONIS trials. There was a lower incidence of hyperthyroidism in the dronedarone group (8.4 vs 14.1%; $p = 0.002$) and a higher incidence of serum creatinine elevation (2.4 vs 0.2%; $p = 0.004$) when compared with the placebo group [14]. In the ATHENA trial (n = 4628, mean follow-up: 21 months) early therapy discontinuation rates has been reported as 30.2% in the dronedarone group and 30.8% of patients in the placebo group. Adverse events were the main reasons for discontinuation in 12.7% of patients in the dronedarone group compared to 8.1% in the placebo group ($p < 0.001$). Although incidences of bradycardia, QT-interval prolongation, gastrointestinal events, rash and serum creatinine elevation were significantly higher in the dronedarone group, pulmonary symptoms, interstitial lung disease and abnormalities of thyroid 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 [101]. 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. 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.

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