Drugs 2009; 69 (12): 1647-1663
0012-6667/09/0012-1647/$55.55/0

Dronedarone

Sheridan M. Hoy and *Susan J. Keam*

Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Philadelphia, Pennsylvania, USA

Contents

Abstract

▲ Oral dronedarone is a non-iodinated benzofurane derivative structurally related to amiodarone. Although it is considered a class III antiarrhythmic agent like amiodarone, it demonstrates multi-class electrophysiological activity.

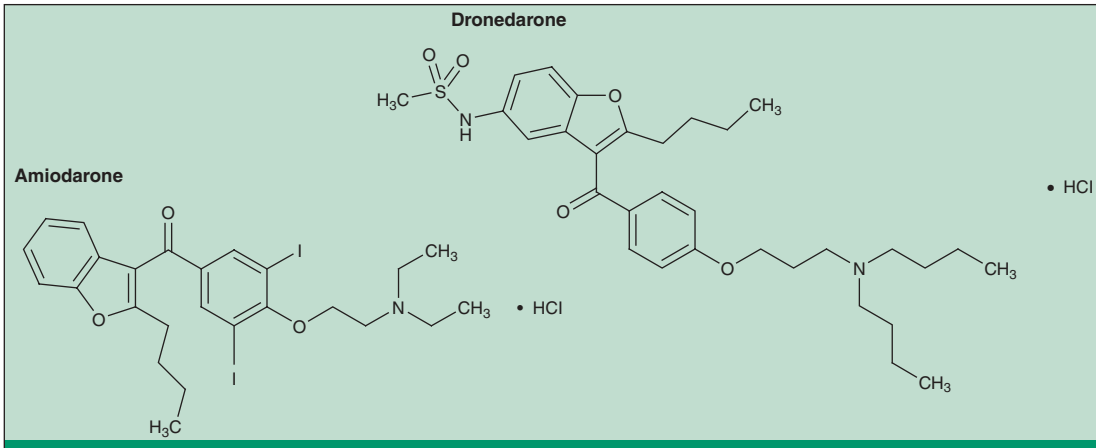
▲ Data from the ATHENA study demonstrated that patients receiving oral dronedarone 400 mg twice daily for 12–30 months had a significantly lower risk of experiencing first hospitalization due to a cardiovascular event or death from any cause than those receiving placebo.

▲ Dronedarone exhibited rate- and rhythm-controlling properties in patients with atrial fibrilation (AF) or atrial flutter, significantly reducing the risk of a first recurrence of AF versus placebo following 12 months' therapy in the ADONIS and EURIDIS studies.

▲ In the ERATO study, dronedarone was also significantly more effective than placebo in terms of ventricular rate control. Furthermore, the beneficial effects of oral dronedarone on ventricular rate control were maintained during exercise and sustained with continued therapy.

▲ Oral dronedarone was generally well tolerated in the treatment of adult patients with AF and/or atrial flutter in clinical studies. The incidence of diarrhoea, nausea, bradycardia, rash and QT-interval prolongation was significantly higher with oral dronedarone than placebo in the large ATHENA study; however, serious cardiac-related adverse events were observed in <1% of oral dronedarone recipients.

Features and properties of dronedarone (SR33589; Multaq®)	
Indication	
To reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter, with a recent episode of AF/atrial flutter and associated cardiovascular risk factors (i.e. age >70 years, hypertension, diabetes mellitus, prior cerebrovascular accident, left atrial diameter ≥50 mm or left ventricular ejection fraction <40%), who are in sinus rhythm or who will be cardioverted	
Mechanism of action	
Inhibits calcium, potassium and sodium channels, demonstrates non-competitive anti-adrenergic activity and prolongs the action potential duration	
Dosage and administration	
Dosage	400 mg twice daily with meals
Route of administration	Oral
Steady state pharmacokinetic parameters of oral dronedarone 400 mg twice daily (mean values unless otherwise stated)	
Maximum plasma concentration (C_{max})	111 ng/mL
Median time to C_{max}	5 h
Area under the plasma concentration-time curve from time zero to 12 h	798 ng • h/mL
Most frequent treatment-emergent adverse events in the ATHENA study	
Diarrhoea, dizziness, nausea, dyspnoea	



Dronedarone and Amiodarone

The management of patients with atrial fibrillation (AF) comprises ventricular rate- and/or sinus rhythm-control strategies in conjunction with antithrombotic therapy.[1] Up to 50% of patients with new onset AF spontaneously convert to a sinus rhythm within the first 24 hours; lack of spontaneous conversion necessitates the use of electrical or pharmacological cardioversion, although the effectiveness of the latter is greatly reduced in the face of persistent (>7 days) AF.[1] The high likelihood of a recurrence of AF may necessitate continuous antiarrhythmic therapy in the majority of patients;[1,2] the beneficial effects achieved with maintaining sinus rhythm need to be balanced with the adverse event profile of the chosen antiarrhythmic therapy.[3]

One class III agent utilized in the control of AF is amiodarone.[2,3] While efficacious, amiodarone at high doses or after extended use has an unfavourable adverse event profile, inducing, among other adverse events, pulmonary fibrosis, hepatic and thyroid dysfunction, gastrointestinal, neurological and dermatological disorders, and elevations in plasma digoxin and warfarin levels when coadministered.[1-4] The utilization of amiodarone has therefore been restricted to patients with clinically significant heart disease for whom alternative therapies have not been successful.[1] Currently, optimal long-term efficacy and tolerability with an antiarrhythmic agent has yet to be achieved.[2]

Dronedarone is a novel non-iodinated benzofurane derivative structurally related to amiodarone.[5] The omission of the iodine moiety is intended to minimize the likelihood of non-target-organ (e.g. thyroid) adverse events, while the addition of the methylsulfonamide group is aimed at reducing lipophilicity and, thus, the likelihood of neurotoxic adverse events.[6]

This article reviews the pharmacological properties of dronedarone (Multaq®), focusing on its efficacy and tolerability in the treatment of patients with non-permanent AF. Medical literature on the use of dronedarone in non-permanent AF was identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Wolters Kluwer Health | Adis). Additional references were identified from the reference lists of published articles.

1. Pharmacodynamic Profile

This section provides an overview of the pharmacodynamic properties of dronedarone. Unless otherwise stated, the data discussed in this section are fully published.

Mechanism of Action

• The predominate mechanism of action of dronedarone is the inhibition of potassium channels and the prolongation of the action potential duration

(APD).[5] It is therefore considered, like amiodarone, to primarily be a class III antiarrhythmic agent, although both drugs demonstrate multiclass electrophysiological activity. Dronedarone also inhibits sodium (at rapid pacing rates) [class I] and calcium (class IV) channels and demonstrates non-competitive anti-adrenergic activity (class II).[5,7] However, the contribution of each of these antiarrhythmic properties to the clinical effect of dronedarone is as yet unknown.[8]

- *In vitro* data indicate that dronedarone inhibits various potassium currents (including transmembrane delayed rectifier, ultrarapid delayed rectifier, inward rectifier and transient outward potassium currents)[9,10] in human atrial myocytes[9] and guinea pig ventricular cells,[10] inhibits the carbochol-induced muscarinic acetylcholine receptor-operated potassium channel in a concentration-dependent manner in isolated guinea pig atrial myocytes (concentration required for 50% inhibition was ≈100-fold lower than that of amiodarone [≈10 nmol/L vs ≈1 μmol/L])[11] and induces voltage-independent inhibition of acetylcholine-activated potassium currents in rabbit sinoatrial myocytes.[12] Dronedarone is also an antagonist of cloned HERG potassium channels *in vitro*.[13]
- Concentration-dependent inhibition of sodium currents has been demonstrated utilizing dronedarone *in vitro* in human atrial myocytes[14] and isolated guinea pig ventricular cells.[10,15]
- Concentration-dependent inhibition by dronedarone of L-type calcium channels has also been demonstrated *in vitro* in guinea pig ventricular cells.[10] Reductions in contraction amplitudes and free intracellular calcium levels have been observed in guinea pig ventricular cells; resting membrane potential was not affected.[10]
- Intravenous dronedarone partially inhibited activation of the adrenoceptor system by catecholamines in an intact canine model (attenuating epinephrine-induced increases in blood pressure [BP] and inhibiting isoprenaline-induced increases in heart rate and reductions in BP), suggesting an inhibition of α-, β_1- and β_2-adrenoceptor receptors.[16] In a canine model of healed myocardial infarction, dronedarone and amiodarone displayed a generally similar level of antiadrenergic activity, dose-dependently lowering heart rate, both at rest and following exercise.[17] Left ventricular function was not impaired by either dronedarone or amiodarone.[17]

Cardiovascular Effects

- The electrophysiological profile of dronedarone *in vitro* and in animal models is generally similar to that of amiodarone.[18-22] For instance, in *ex vivo* studies in rabbit myocardium, significant ($p < 0.05$) and/or dose-dependent reductions versus control in APD at 50% (APD_{50}) and 90% (APD_{90}) repolarization, effective refractory period (ERP) and the maximum slope of the action potential (V_{max}) were observed following acute superfusion with dronedarone or amiodarone in an atrial model.[18,19]
- Significant ($p < 0.05$) prolongation of the APD_{90} and ERP (independent of the frequency of stimulation of the atria) were observed with 4 weeks of oral dronedarone and oral amiodarone therapy versus control in rabbit atrial myocardium.[18]
- In rabbit ventricular myocardium, significant ($p < 0.005$) prolongation of the ventricular APD, as a function of dose and cycle length, slowing of sinoatrial node automaticity (as observed by prolongation of spontaneous cycle length) and increases in RR, QT and corrected QT (QTc) intervals were observed with 3 weeks of oral dronedarone and oral amiodarone therapy versus control.[19] In general, oral dronedarone was significantly ($p < 0.005$) more effective than oral amiodarone in prolonging ventricular APD and spontaneous cycle length.[19]
- A significant ($p < 0.05$ vs control) slowing of sinoatrial node automaticity (as evidenced by a reduction in the action potential amplitude, the slope of phase 4 depolarization and the spontaneous beating rate) was also observed following the acute administration of dronedarone and amiodarone in a rabbit atrial myocardium model.[23]
- High doses (100 mg/kg/day) of oral dronedarone[18,19] and oral amiodarone[19] significantly ($p < 0.05$) depressed V_{max} in rabbit atrial[18]

or ventricular[19] myocardium, indicating an effect on sodium currents.

- In another *ex vivo* study in canine ventricular myocytes, dronedarone exhibited generally similar cardiac electrophysiological effects to amiodarone following acute superfusion, with inhibition of the rapid component of the delayed rectifier potassium current and the L-type calcium current.[22] However, unlike amiodarone, no significant prolongation of the APD or QTc interval in canine papillary muscle or Purkinje fibres was observed versus control following 4 weeks of oral dronedarone therapy.[22]
- Results in canine[21] or rat[24-26] cardiac models confirmed the antiarrhythmic effects of dronedarone seen in *in vitro* and *ex vivo* studies. For example, oral or intravenous dronedarone demonstrated ventricular antiarrhythmic activity *in vivo*, reducing the incidence of mortality, ventricular fibrillation and ventricular tachycardia in an intact rat heart model of ischaemia and reducing the incidence of mortality and ventricular fibrillation in an intact rat model of reperfusion.[25] Results with oral or intravenous amiodarone were generally consistent with those of dronedarone.[25] In addition, dronedarone and amiodarone displayed cardioprotective effects in an isolated rat heart model damaged by ischaemia or reperfusion.[26]
- In various animal cardiac models,[27-29] dronedarone did not appear to induce arrhythmias (such as *torsade de pointes*),[27,28] and reduced premature ventricular complexes, ventricular tachycardia and ventricular fibrillation induced during the early phase of coronary artery occlusion.[29]
- In isolated guinea pig myocytes perfused with potassium, the concentration-dependent induction of coronary vasodilation by both dronedarone and amiodarone involved nitric oxide.[30] However, dronedarone, unlike amiodarone, induces a relaxant effect refractory to the nitric oxide synthase pathway, possibly because of its calcium antagonistic activity.[30]
- Oral dronedarone had no effect on plasma thyroid hormone levels in isolated and thyroxine-induced hyperthyroid rat heart models.[31] In contrast, oral amiodarone therapy resulted in significant ($p < 0.05$) elevations in plasma thyroxine (T4), reserve triiodothyronine (rT3) and T4/T3 levels versus control in normal rat heart models, but had no significant effect in the thyroxine-induced hyperthyroid rat heart model.[31] Neither dronedarone nor amiodarone affected basal functional parameters or ischaemic contracture in normal or thyroxine-induced hyperthyroid rat heart models.[31] Furthermore, in the normal rat heart model, neither treatment altered post-ischaemic functional recovery.[31]
- Differences between dronedarone and amiodarone in thyroid hormone receptor-dependent gene expression have been observed in a recent rat heart model.[32] Dronedarone and amiodarone reduced thyroid receptor (TR)-α1 and -β1 expression in the right atrium, potentially contributing to heart rate reduction, and TRβ1 expression in the left ventricular wall.[32] However, amiodarone, but not dronedarone, increased TRα1 expression in the left ventricular wall.[32]
- Oral dronedarone exerts a dose-dependent effect on PR and QTc intervals but not heart rate.[8] In a study in healthy volunteers who received oral dronedarone dosages of up to 1600 mg once daily or 800 mg twice daily for 14 days and 1600 mg twice daily for 10 days, elevations in the PR interval of 5 ms and up to 50 ms were observed in the 400 mg twice daily and 1600 mg twice daily treatment groups.[8] Elevations in the QTc interval were 10 ms and up to 25 ms in the respective treatment groups.[8] No apparent effect on heart rate was observed in the 400 mg twice daily group; subjects receiving oral dronedarone 800 mg twice daily had reductions in heart rate of ≈4 beats/min.[8]
- Circadian variation of the heart rate and QT intervals does not appear to be affected by dronedarone.[33] In general, prolongation of RR, QT and QTc intervals, as a function of dose, was observed with oral dronedarone versus placebo or baseline in a randomized, double-blind study in which 41 healthy male volunteers received oral dronedarone 800–1600 mg twice daily or placebo for 10 days.[33] The prolongation of the QT and QTc intervals was determined to be independent of the circadian rhythm.[33]

Table I. Study acronyms

Acronym	Definition	Countries (no. of patients randomized)
ADONIS[38]	American-Australian-African trial with DrONedarone In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm	Argentina, Australia, Canada, South Africa, US (625)
ANDROMEDA[35]	ANtiarrhythmic trial with DROnedarone in Moderate to severe CHF Evaluating morbidity DecreAse	6 EU countries (627)
ATHENA[39,40]	A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid (twice daily) for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter	37 countries worldwide (4628)
DAFNE[36]	Dronedarone Atrial FibrillatioN study after Electrical cardioversion	11 countries worldwide (270)
ERATO[41]	Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation	9 EU countries (174)
EURIDIS[38]	EURopean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maIntenance of Sinus rhythm	12 EU countries (612)

Renal Effects

- Data from a randomized, double-blind, crossover, placebo-controlled, phase I study indicated that dronedarone 400 mg twice daily reduced renal creatinine clearance by ≈18% versus placebo ($p < 0.05$), without affecting renal sinistrin clearance (indicating no effect on glomerular filtration rate [GFR]), the excretion of sodium and potassium, or renal plasma flow in healthy male volunteers ($n = 12$).[34] These results suggest that increases in serum creatinine with dronedarone may be a result of the partial inhibition of the tubular organic cation transporter system, rather than a decline in renal function. Consequently, there is the potential for interaction with cationic drugs.[34]

2. Pharmacokinetic Profile

Limited pharmacokinetic data are available for dronedarone. Discussion in this section focuses predominately on data from the US FDA prescribing information,[8] supplemented with data from the FDA briefing document.[35] Data from two fully published, randomized, double-blind, placebo-controlled studies,[36,37] including the dose-finding DAFNE study[36] (for study acronym definitons, see table I) in which patients with persistent AF scheduled for elective electrical cardioversion received oral dronedarone 400, 600 or 800 mg twice daily or placebo for at least 5–7 days (see section 3 for further dosage and design details), are also reviewed.

Oral dronedarone is poorly absorbed in the fasted state; however, administration with food increases absorption.[8,35] Dronedarone is recommended to be taken with food, and its pharmacokinetics have been mainly assessed in the fed state.[8,35]

Absorption and Distribution

- The pharmacokinetics of dronedarone are non-linear, as evidenced by the more than dose-proportional increases in mean maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) values.[8,35] A 2-fold increase in the dronedarone dose leads to an approximately 2.5- to 3-fold increase in C_{max} and AUC values.[8]
- Steady state conditions for oral dronedarone 400 mg twice daily are reached within 4–8 days.[8] After multiple doses of dronedarone 400 mg twice daily with concomitant food consumption, the mean C_{max} was 111 ng/mL, the median time to C_{max} was 5 hours (range 3–6 hours) and the mean AUC from time 0 to 12 hours was 798 ng • h/mL in healthy volunteers.[35] The mean accumulation ratio for a dronedarone 400 mg twice-daily dosage was 2.6–4.5.[8]
- Administration of dronedarone with food increased the absolute bioavailability of the drug ≈2- to 5-fold compared with the fasted state; absolute bioavailability of dronedarone was approximately 15% following administration with a high-fat meal.[8,35]

- *In vitro*, more than 98% of dronedarone and its *N*-debutyl metabolite are bound, in a nonsaturable manner, to plasma proteins (mainly albumin).[8]
- The volume of distribution at steady state following the administration of intravenous dronedarone was ≈1400 L.[8] The apparent volume of distribution at steady state (during the terminal phase) following the administration of oral dronedarone 400 mg twice daily in healthy volunteers was 22 800 L.[35]
- In animal studies, dronedarone appears to be widely distributed throughout the body, including the kidney, liver, lung, myocardium and spleen.[35] Dronedarone also crossed the blood-brain and placental barriers in animal studies and was excreted into breast milk.[35]
- The steady-state pharmacokinetics of dronedarone in patients with AF or atrial flutter were similar to those in healthy volunteers, based on comparisons between a pharmacokinetic study in healthy volunteers and data from the ANDROMEDA study and a population pharmacokinetic analysis of patients in phase II and III clinical studies.[35]

Metabolism and Elimination

- Dronedarone primarily undergoes hepatic metabolism via the cytochrome P450 (CYP) 3A isoenzyme.[8,35] Compared with intravenous administration, a first-pass effect is observed following oral administration.[8,35] The main metabolite formed after first-past metabolism is the *N*-debutyl metabolite, which has pharmacological activity 3- to 10-fold lower than that of dronedarone.[8,35] The amount of the *N*-debutyl metabolite formed after oral administration is dose-dependent, suggesting that the first-pass effect is saturable.[35]
- Following oral administration, the pharmacokinetic profile of the *N*-debutyl metabolite at steady state is similar to that of dronedarone.[8,35] However, it is unlikely to contribute significantly to the antiarrhythmic activity of dronedarone because of its lower levels of pharmacological activity.[35] In the DAFNE study, the mean *N*-debutyl metabolite : dronedarone ratio was 0.6, regardless of dose.[36]
- Plasma clearance was 130–150 L/h following intravenous dronedarone administration;[8,35] the mean apparent total clearance at steady state following the oral administration of multiple doses of dronedarone 400 mg twice daily was 517 L/h.[35] The mean apparent total clearance values on both days 1 and 14 were approximately 30% higher with dronedarone 400 mg twice daily than with dronedarone 800 mg twice daily, the cause of which is unclear (but may possibly be due to competing metabolic processes).[35]
- Furthermore, the saturable element of metabolism does not appear to be the main reason for the nonlinearity of dronedarone pharmacokinetics, because the apparent terminal elimination half life at steady state did not vary across a dosage range of 200–800 mg twice daily.[35]
- Dronedarone is eliminated from the plasma in a biphasic manner,[35] with an elimination half-life ($t_{½\beta}$) of 13–19 hours following intravenous administration.[8] The $t_{½\beta}$ after oral administration appeared to be both time and dose dependent.[35]
- Oral dronedarone is predominately (84%) excreted in the faeces as metabolites; minimal (≈6%) excretion, mainly as metabolites, occurs via the urine.[8,35]

Special Populations

- Exposure to dronedarone is approximately 2-fold higher in Japanese males than Caucasian males following a single 400 mg dose.[8,35] Dronedarone exposure is also higher (≈23%) in patients aged ≥65 years than those aged <65 years in clinical studies of dronedarone, and higher in females (≈30%) than males.[8]
- As dronedarone primarily undergoes hepatic metabolism, the pharmacokinetics of dronedarone may be altered in patients with hepatic impairment. Although no statistically significant between-group difference in dronedarone exposure was observed in patients with moderate hepatic impairment and healthy volunteers who both received dronedarone 400 mg twice daily for 7 days, patients with moderate hepatic impairment exhibited numerically higher dronedarone exposure values and a highly variable

coefficient of variation (>70%), indicating the potential for supra-therapeutic concentrations.[35]

- The pharmacokinetics of dronedarone in patients with severe hepatic impairment has not yet been assessed; however, the administration of dronedarone to patients with severe hepatic impairment is contraindicated.[8]
- Elevated plasma creatinine levels (as expected from the partial inhibition of tubular cationic transport [section 1]) were observed in elderly patients with normal or impaired renal function following the administration of dronedarone 400 mg twice daily for 14 days.[35] The magnitude of creatinine changes was independent of renal function[35] and the pharmacokinetics of dronedarone were not altered by the presence of mild, moderate or severe renal impairment.[8]

Drug Interactions

- Dronedarone demonstrates no significant inhibitory potential towards the major CYP isoenzymes; it is, however, a moderate inhibitor of CYP3A and CYP2D6.[8,35] It is expected that the levels of dronedarone will be affected by CYP3A inducers and inhibitors, and that dronedarone will affect CYP3A substrates.[8]
- Concurrent treatment with dronedarone and a CYP3A inducer, such as carbamazepine, phenobarbital, phenytoin, rifampicin (rifampin) and St John's Wort (hypericum), leads to reduced dronedarone exposure and is not recommended.[8]
- Coadministration with the potent CYP3A inhibitor ketoconazole results in a 17-fold increase in dronedarone exposure and a 9-fold increase in C_{max}.[8] As a consequence, the concurrent administration of dronedarone with potent CYP3A inhibitors, such as clarithromycin, ketoconazole, nefazodone and ritonavir, is contraindicated.[8] Concurrent therapy with moderate CYP3A inhibitors, such as diltiazem, grapefruit juice and verapamil, leads to elevated (1.4- to 3-fold) dronedarone exposures; concomitant therapy with dronedarone and grapefruit juice is not advised.[8]
- The concomitant administration of dronedarone and drugs or herbal products that prolong the QT interval, such as phenothiazine antipsychotics and tricyclic antidepressants, may induce *torsade de pointes*, and is thus contraindicated.[8]
- Dronedarone has the potential to inhibit the transportation of P-glycoprotein (PGP) and, thus, increase the exposure of PGP substrates (e.g. digoxin).[8] Furthermore, the electrophysiological effects of dronedarone (e.g. reduced atrioventricular node conduction) may be potentiated by digoxin.[8] Thus, caution and/or the monitoring of patients is advised (as dose adjustments of the concomitant drug may be required) with the coadministration of dronedarone and digoxin.[8]
- The concomitant administration of dronedarone and warfarin resulted in no clinically significant increase in the international normalization ratio (INR) in healthy volunteers; furthermore, no excess risk of bleeding in patients with AF or atrial flutter was observed following concomitant dronedarone and oral anticoagulant therapy.[8] Therefore, no additional INR monitoring over that which is normally required for warfarin is advised.[8]

3. Therapeutic Efficacy

The therapeutic efficacy of oral dronedarone in patients with AF and/or atrial flutter has been assessed in the randomized, double-blind, placebo-controlled, multicentre, phase II, dose-finding DAFNE study[36] and in four randomized, double-blind, parallel-group, placebo-controlled, multicentre, phase III studies of 6–30 months' duration: ATHENA,[39] ERATO,[41] ADONIS[38] and EURIDIS.[38] All studies are fully published.

Preliminary data from a *post hoc* subanalysis[42] of the ATHENA study[39] and a meta-analysis[43] of the five clinical studies[36,38,39,41] (both currently available only in abstract form) are also discussed.

DAFNE

The DAFNE study was a randomized, double-blind, placebo-controlled, multinational, dose-ranging study of dronedarone 800–1600 mg/day in patients with persistent AF scheduled for elective electrical cardioversion.[36] Eligible patients were

aged 21–85 years, had persistent AF of 72 hours to 12 months' duration and had undergone effective anticoagulation at least 3 weeks before randomization. Patients were permitted to have coexisting ischaemic or hypertensive heart disease, dilated cardiomyopathy or valvular anomalies (with no significant haemodynamic dysfunction). Those patients who had not converted to a sinus rhythm after 5–7 days of dronedarone therapy were treated with electrical cardioversion. Patients who were successfully cardioverted with either method continued to receive dronedarone or placebo for 6 months; therapeutic anticoagulation was continued for at least 4 weeks after cardioversion.

The main exclusion criteria were more than two cardioversions in the previous 6 months, atrial flutter as the presenting arrhythmia, unstable angina or recent myocardial infarction, other ECG conduction abnormalities, implanted cardioverter defibrillator, New York Heart Association (NYHA) class III or IV congestive heart failure (CHF), left ventricular ejection fraction (LVEF) <35% and large changes in serum potassium levels.[36]

At baseline, the mean patient age was 62–65 years; 68% of patients were male, 58% had recurrent AF (mean AF duration of 82–122 days), 50% had hypertension, 21% had coronary artery disease, 38% had valvular disease and 16% had heart failure.[36]

The primary efficacy outcome was time to first documented AF recurrence.[36] Analyses were conducted in 199 patients who received maintenance therapy after successful cardioversion. In this population, patients received twice-daily dronedarone 400 mg (n = 54), 600 mg (n = 54) or 800 mg (n = 43) or placebo (n = 48) for 6 months.[36]

- The dose-finding DAFNE study determined that oral dronedarone 400 mg twice daily was the optimal dosage in patients with persistent AF.[36] The median time to a documented recurrence of AF (primary endpoint) was 60 days in the oral dronedarone 400 mg twice daily treatment group (n = 54) and 5.3 days in the placebo group (n = 48) [relative risk reduction 0.55; 95% CI 0.28, 0.72; p = 0.001].[36] No significant difference in the median time to a documented recurrence of AF was observed between dronedarone 600 (n = 54) or 800 (n = 43) mg twice daily (no data reported) and placebo, indicating a lack of dose effect.[36]

ATHENA

ATHENA was a large, randomized, double-blind, placebo-controlled, multinational study that assessed the efficacy of longer-term dronedarone therapy in high-risk patients with a history of paroxysmal or persistent AF or atrial flutter.[39,40] Patients aged 70–74 years were enrolled if they had at least one cardiovascular risk factor, whereas those aged ≥75 years were eligible with or without additional cardiovascular risk factors. The study had initially enrolled patients aged <70 years of age, but because of a lower-than-expected overall mortality rate, a protocol amendment half-way through the 18-month enrolment period excluded such patients, in order to enhance the risk profile.[39]

Other eligibility criteria included recent (within 6 months) ECG evidence of non-permanent AF/atrial flutter. Patients in sinus rhythm at study entry were required to have converted spontaneously or after electrical or pharmacological cardioversion, while those in AF or atrial flutter at study entry underwent cardioversion after anticoagulation. Patients were stratified according to the presence or absence of AF or atrial flutter at randomization.[39,40]

Patients were excluded if they had permanent AF, other ECG conduction abnormalities, recent decompensated heart failure, NYHA class IV CHF, planned major surgery, a calculated baseline GFR of <10 mL/min, a baseline potassium level of <3.5 mmol/L (unless corrected) or required concomitant class I or III antiarrhythmics.[39,40]

At baseline in the ATHENA study, the mean age was 72 years; 19% of patients were aged <65 years, 40% were aged 65–74 years and 42% were aged ≥75 years. Approximately half of the patients (47%) were female, 25% had AF or atrial flutter, 86% had hypertension, 60% had structural heart disease, 30% had coronary heart disease, 21% had NYHA class II or III CHF, and most patients (88%) had normal left ventricular function (LVEF ≥45%). The most frequent

baseline therapies were β-adrenoceptor antagonists (β-blockers) [71% of patients], ACE inhibitors or angiotensin receptor antagonists (ARBs) [70%], vitamin K antagonists (60%), aspirin (44%) and HMG CoA reductase inhibitors (statins) [39%].[39] The mean duration of follow-up was 21 months (median duration 22 months; maximum 2.5 years).[39]

Patients were randomized to receive dronedarone 400 mg twice daily (n = 2301) or placebo (n = 2327), with a minimum follow-up duration of 12 months. The primary efficacy endpoint was the incidence of first hospitalization due to cardiovascular events or death from any cause during the study, and the secondary endpoints were the incidences of death from any cause, cardiovascular death and first cardiovascular hospitalization.[39,40] Analyses were conducted in the intent-to-treat (ITT) population.[39]

- Therapy with oral dronedarone 400 mg twice daily was effective in reducing the risk of first hospitalization due to a cardiovascular event or death in patients with AF or atrial flutter in the ATHENA study (primary endpoint) [figure 1].[39] Following 12–30 months' therapy, 29.3% and 2.6% of oral dronedarone recipients were hospitalized due to a cardiovascular event or died, compared with 36.9% and 2.5% of placebo recipients.[39]
- The risk of death from cardiovascular causes and first hospitalization due to cardiovascular events in ATHENA was also significantly reduced with oral dronedarone versus placebo (figure 1).[39] However, no significant difference was observed between the two treatment groups with regard to the risk of death from any cause (figure 1).[39]
- In the ATHENA study, the significant reduction in the risk of first hospitalization for atrial fibrillation (14.6% vs 21.9%; hazard ratio [HR] 0.63; 95% CI 0.55, 0.72; $p < 0.001$) accounted for most of the observed reduction in the risk of first hospitalization due to cardiovascular events.[39] A significant reduction in the risk of first hospitalization for acute coronary syndrome (2.7% vs 3.8%; HR 0.70; 95% CI 0.51, 0.97; $p < 0.05$) also contributed.[39]
- *Post hoc* subgroup analyses indicated that dronedarone was more effective than placebo in terms of the primary efficacy endpoint, regardless of baseline characteristics, including patient age (<75 years or ≥75 years), sex, the presence or absence of AF or atrial flutter, structural heart disease, CHF or impaired LVEF, and the use of ACE inhibitors or ARBs, or β-blockers.[39]
- In patients with AF and NYHA Class III CHF and/or a LVEF of <35%, dronedarone 400 mg twice daily (n = 91) had no significant adverse effect on the risk of death relative to those receiving placebo (n = 109) [13.2% vs 19.3%; HR 0.66; 95% CI 0.32, 1.34], according to a *post hoc* subanalysis[42] of data from the ATHENA study.[39] A significant reduction in the risk of experiencing the primary outcome occurred in patients with AF and NYHA Class III CHF receiving oral dronedarone relative to those receiving placebo (44.0% vs 65.1%; HR 0.56; 95% CI 0.39, 0.82; $p < 0.005$).[42]
- Furthermore, no significant between-group differences were observed between dronedarone and

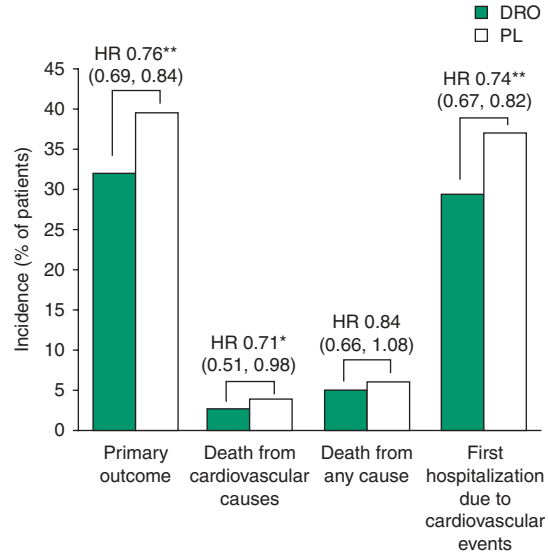


Fig. 1. Efficacy of oral dronedarone (DRO) in patients with atrial fibrillation (AF) or atrial flutter. Results of the randomized, double-blind, parallel-group, placebo (PL)-controlled, multicentre, phase III ATHENA study; analyses are of intent-to-treat data.[39] Patients with AF or atrial flutter received oral DRO 400 mg twice daily (n = 2301) or PL (n = 2327) for 12–30 months. The primary outcome was the first hospitalization due to a cardiovascular event or death from any cause. 95% confidence intervals for the hazard ratio (HR) are shown in parentheses. * $p < 0.05$, ** $p < 0.001$ vs PL.

placebo in the incidence of patients who (following randomization) were observed to deteriorate to NYHA Class IV CHF or in the risk of experiencing the primary endpoint (in these patients).[42]

ADONIS and EURIDIS

The ADONIS and EURIDIS studies were two identical, 12-month, randomized, double-blind, parallel-group, placebo-controlled, multinational studies of dronedarone for the maintenance of sinus rhythm in patients with AF or atrial flutter that were conducted at EU and non-EU sites.[38] Patients aged ≥21 years were enrolled if they had experienced at least one episode of AF in the preceding 3 months and were in sinus rhythm for ≥1 hour prior to randomization. Patients were excluded if they had permanent AF (duration ≥12 months), other ECG conduction abnormalities, NYHA class III or IV CHF, a serum creatinine level ≥150 μmol/L, severe electrolyte abnormalities and clinically significant noncardiac disorders associated with AF, or required concomitant class I or III antiarrhythmics. Prior treatment with amiodarone was permitted, provided it was discontinued prior to enrolment.[38]

At baseline, across both trials, the mean age was 63 years; 69% of patients were male, 57% had hypertension, 41% had structural heart disease, 22% had coronary artery disease, 18% had CHF, 16% had valvular disease and 11% had atrial flutter.[38] The most common concomitant cardiovascular therapies at baseline were oral anticoagulants (70% of patients), β-blockers (excluding sotalol) [56%], ACE inhibitors (39%), long-term antiplatelet therapy (39%) and statins (32%). The most frequent previous antiarrhythmic therapies were amiodarone (30% of patients) and sotalol (26%).[38]

Patients were randomized to receive dronedarone 400 mg twice daily (n = 417 [ADONIS] and 411 [EURIDIS]) or placebo (n = 208 and 201), with a follow-up duration of 12 months.[38] The primary efficacy endpoint was time to first documented recurrence of AF; secondary endpoints were symptoms related to AF during monitoring and mean ventricular rate during first recurrence. Analyses were conducted in the modified ITT population.[38]

- Oral dronedarone exhibited rate-controlling properties in patients with AF or atrial flutter in the ADONIS and EURIDIS studies.[38] The median time from randomization to a documented recurrence of AF (primary endpoint) with oral dronedarone 400 mg twice daily was 158 days in the ADONIS study (n = 417) and 96 days in the EURIDIS study (n = 411). Corresponding median times with placebo were 59 and 41 days (n = 208 and 201).[38] In pooled data from the two studies, the median time from randomization to a documented recurrence of AF were 116 and 53 days in patients in the oral dronedarone (n = 828) and placebo (n = 409) treatment groups.[38]
- Compared with placebo, oral dronedarone 400 mg twice daily significantly reduced the risk of a first recurrence of AF in the ADONIS and EURIDIS studies following 12 months' therapy (figure 2).[38] The risk of a first recurrence of AF with oral dronedarone was also significantly lower than that with placebo in a pooled analysis of the two studies (figure 2).[38]
- A preplanned subanalysis excluding patients with an exposure period of less than 5 days prior to the occurrence of the primary endpoint or treatment cessation found a significant ($p < 0.05$) reduction in

Fig. 2. Efficacy of oral dronedarone (DRO) in patients with atrial fibrillation (AF) or atrial flutter. Incidence of a first recurrence of AF in the randomized, double-blind, parallel-group, placebo (PL)-controlled, multicentre, phase III ADONIS and EURIDIS studies; analyses are of modified intent-to-treat data.[38] Patients with AF or atrial flutter received oral DRO 400 mg twice daily (ADONIS: n = 417; EURIDIS: n = 411) or PL (ADONIS: n = 208; EURIDIS: n = 201) for 12 months. 95% confidence intervals for the hazard ratio (HR) are shown in parentheses. * $p = 0.01$, ** $p = 0.002$, *** $p < 0.001$ vs PL.

the risk of adjudicated recurrence of AF or atrial flutter from day 5 to 12 months in dronedarone versus placebo recipients; 51.3% versus 62.6% of patients (HR 0.74; 95% CI 0.57, 0.96) in ADONIS (n = 327 and 146) and 56.4% versus 69.5% (HR 0.71; 95% CI 0.56, 0.91) in EURIDIS (n = 307 and 148).[38]

- The risk of symptomatic AF recurrence (specific details of the patient population not defined) was significantly reduced in oral dronedarone 400 mg twice daily versus placebo recipients in both ADONIS (n = 327 and 146) [38.3% vs 44.5%; HR 0.74; 95% CI 0.57, 0.96; p = 0.02] and EURIDIS (n = 307 and 148) [37.1% vs 47.5%; HR 0.70; 95% CI 0.54, 0.90; p = 0.006]) and in the pooled analysis of the two studies (37.7% vs 46.0% [n = 634 and 294]; HR 0.71; 95% CI 0.60, 0.86; p < 0.001).[38] The majority of documented first recurrence AF episodes were symptomatic; the pattern of symptoms did not differ between the treatment groups.[38]
- Ventricular rates during the recurrence of AF were significantly lower with oral dronedarone than with placebo.[38] Patients receiving oral dronedarone 400 mg twice daily exhibited significantly (p < 0.001) lower mean ventricular rates during the first adjudicated recurrence of AF (ADONIS: n = 188; EURIDIS: n = 199) than those receiving placebo (ADONIS: n = 102; EURIDIS: n = 117) in both the ADONIS (104.6 vs 116.6 beats/min) and EURIDIS (102.3 vs 117.5 beats/min) studies.[38] A significant difference between the two treatment groups was also observed in the pooled analysis of the two studies (103.4 and 117.1 beats/min in oral dronedarone and placebo recipients; p < 0.001).[38]
- Therapy with oral dronedarone was associated with a significant reduction in heart rate and prolongation of QT interval in patients in sinus rhythm.[38] In pooled data from the ADONIS and EURIDIS studies, dronedarone 400 mg twice daily recipients (n = 828) showed significantly (all p < 0.0001 vs placebo) greater changes from baseline than placebo recipients in mean heart rate (by 6.8% [4.4 beats/min]), mean QT interval (23.4 ms) and mean QTc interval (8.8 ms); no significant changes occurred in QRS duration.[38]
- In a *post hoc* analysis of the individual ADONIS and EURIDIS studies, oral dronedarone 400 mg twice daily reduced the risk of hospitalization or death at 12 months to a significantly (p < 0.05) greater extent than placebo in the EURIDIS but not in the ADONIS study.[38] However, when the data were pooled, the overall risk reduction (HR 0.73; 95% CI 0.57, 0.93) was significant (p = 0.01).[38] *Post hoc* subgroup analyses also showed that oral dronedarone was efficacious in reducing the risk of recurrence of AF or atrial flutter regardless of baseline characteristics, including conversion to sinus rhythm in ≤5 days, heart failure (criteria met), hypertension, left atrial diameter, structural heart disease and previous use of antiarrhythmic drugs, including amiodarone.[38]

ERATO

The ERATO study was a 6-month, randomized, double-blind, placebo-controlled, parallel-group, multinational study that assessed the efficacy of dronedarone in controlling ventricular rate in patients with permanent AF.[41] Patients aged ≥21 years were eligible if they had documented, symptomatic, permanent (duration >6 months) AF for which cardioversion was not an option and a resting ventricular rate of ≥80 beats/min. Patients were excluded if they had a history of unstable angina, other ECG conduction abnormalities, NYHA class III or IV CHF, a baseline potassium level <3.5 mmol/L or were taking other antiarrhythmic agents or potent CYP3A4 inhibitors. Patients on chronic amiodarone therapy underwent a 2-month washout period prior to study entry. Concomitant use of other rate control agents (β-blockers [excluding sotalol], calcium channel antagonists, digoxin) was permitted.[41]

At baseline, the mean age was approximately 65 years, most patients were male (69%), 49% had hypertension, 39% had structural heart disease, 40% had NYHA class I or II CHF, 17% had valvular disease, 17% had coronary artery disease and 10% had dilated cardiomyopathy.[41] The most common concomitant cardiovascular therapies at baseline were oral anticoagulants (88%), β-blockers

(excluding sotalol) [52%], long-term antiplatelet therapy (16%), ACE inhibitors or ARBs (49%), diuretics (44%), digoxin (43%), calcium channel antagonists (23%) and statins (22%). Mean exposure to dronedarone was 157 days.[41]

Patients were randomized to receive dronedarone 400 mg twice daily (n = 85) or placebo (n = 89), in addition to their standard AF therapy, for 6 months.[41] The primary endpoint was the change in mean 24-hour ventricular rate (beats/min) at day 14 compared with day 0. Secondary endpoints included change in mean ventricular rate during maximal and submaximal exercise at day 14 compared with day 0 and change in mean 24-hour ventricular rate at 4 months compared with day 0. Prespecified subgroup analyses stratified primary endpoint results by concomitant baseline therapy. Analyses were conducted in the ITT and per-protocol populations.[41]

- Oral dronedarone was significantly more effective than placebo in ERATO in terms of ventricular rate control in patients with AF.[41] A significant mean change from baseline in the mean 24-hour ventricular rate at day 14 (primary endpoint) was observed in patients receiving oral dronedarone 400 mg twice daily versus those receiving placebo (–11.0 vs +0.7 beats/min; $p < 0.0001$). At baseline, the ventricular rates were 88.8 and 92.3 beats/min in the dronedarone and placebo groups. Prespecified subgroup analyses indicated that the presence or absence of coadministered rate-lowering therapies had no significant effect on the efficacy of dronedarone in terms of the primary endpoint.[41]
- The beneficial effects of oral dronedarone on ventricular rate control were maintained during exercise.[41] Significantly ($p < 0.0001$ vs placebo) greater changes from baseline were observed in dronedarone compared with placebo recipients in the mean ventricular rate during submaximal (–25.6 beats/min) and maximal (–27.4 beats/min) exercise on day 14. Furthermore, the effect on ventricular rate control during exercise does not appear to be associated with a reduction in exercise tolerance.[41]
- Improvements in the ventricular rate observed at day 14 in the ERATO study were sustained with continued oral dronedarone 400 mg twice daily therapy.[41] At 4 months, a significantly ($p < 0.001$ vs placebo) greater mean change from baseline in the mean 24-hour ventricular rate was observed in patients receiving dronedarone than in those receiving placebo, and the effect on the ventricular rate was apparent regardless of the presence of concomitant β-blocker, calcium channel antagonist or digoxin therapy (specific data not reported).[41]

Meta-Analysis

- Oral dronedarone 400 mg twice daily was effective in reducing the risk of a variety of cardiovascular and/or mortality endpoints in patients with AF or atrial flutter, according to a meta-analysis[43] of the DAFNE,[36] ATHENA,[39] ERATO,[41] ADONIS[38] and EURIDIS[38] studies. Compared with placebo, significant reductions in the risk of time to first cardiovascular hospitalization or death (HR 0.76; 95% CI 0.69, 0.84; $p < 0.001$), cardiovascular death (HR 0.71; 95% CI 0.52, 0.96; $p < 0.05$) and sudden death (HR 0.49; 95% CI 0.28, 0.86; $p < 0.05$) were observed with dronedarone therapy.[43]
- No significant between-group difference in the risk of death from any cause was observed between dronedarone and placebo.[43]

4. Tolerability

This section reviews the tolerability data derived from the phase III clinical studies discussed in section 3,[38,39,41] with particular focus on the largest study, ATHENA.[39] Only pooled data were available for the ADONIS and EURIDIS studies,[38] and no statistical analysis was reported for the ERATO study.[41] A pooled analysis, derived from the US manufacturer's prescribing information, is also discussed.[8] Data from a randomized, double-blind, placebo-controlled, parallel-group, multicentre study that was intended to assess the efficacy of oral dronedarone 400 mg twice daily in hospitalized patients with symptomatic heart failure and severe left ventricular systolic dysfunction (ANDROMEDA) are also reviewed.[44]

• Oral dronedarone was generally well tolerated in the treatment of adult patients with AF or atrial flutter in the five clinical studies discussed in section 3.[8] figure 3 presents the incidence of treatment-related adverse events affecting ≥1% of patients and occurring at a greater incidence with dronedarone than placebo across the five studies. The most frequently reported treatment-emergent adverse events were diarrhoea, asthenic conditions, nausea, abdominal pain and bradycardia.[8]

• Treatment-emergent adverse events involving the skin and subcutaneous tissue, including eczema, (allergic dermatitis), pruritus and rash, occurred in 5% of dronedarone (n = 3282) and 3% of placebo (n = 2875) recipients across the five studies; dysgeusia and photosensitivity reactions occurred in <1% of dronedarone recipients.[8]

• Across the five studies, treatment-emergent adverse events led to discontinuation in 11.8% and 7.7% of dronedarone and placebo recipients, with gastrointestinal disorders (3.2% vs 1.8%) and QT interval prolongation (1.5% vs 0.5%) the most common reasons for therapy cessation.[8]

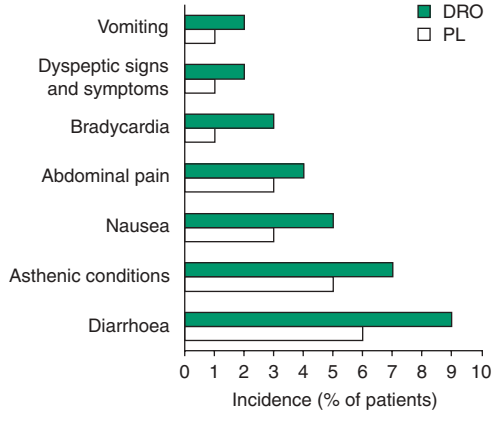


Fig. 3. Tolerability profile of oral dronedarone (DRO) in adult patients with atrial fibrillation or atrial flutter. Incidence of treatment-emergent adverse events affecting ≥1% of patients and occurring at a greater incidence with DRO than placebo (PL) in a pooled analysis[8] of data from recipients of oral DRO 400 mg twice daily (n = 3282) or PL (n = 2875) in the randomized, double-blind, PL-controlled, multicentre, phase II, dose-finding DAFNE study[36] and four randomized, double-blind, parallel-group, PL-controlled, multinational, phase III studies: ATHENA,[39] ERATO,[41] ADONIS[38] and EURIDIS.[38] Patients received oral DRO or PL for a mean of 12 months.

• Elevations of ≥10% in serum creatinine levels during the 5 days after the initiation of therapy occurred in 51% and 21% of patients receiving dronedarone or placebo across the five studies; 28% and 19% of patients in the respective treatment groups experienced prolonged QTc intervals (defined as >450 ms in male and >470 ms in female patients).[8]

• In ATHENA,[39] treatment-emergent adverse events of any severity occurred in most patients receiving dronedarone 400 mg twice daily or placebo (72% vs 69% [n = 2291 and 2313]; $p < 0.05$). Serious treatment-emergent adverse events (an adverse event that resulted in death; was life-threatening, required or prolonged hospitalization; was medically important; resulted in persistent, clinically significant disability or incapacity; or was a congenital anomaly) were reported in 20% of dronedarone and 21% of placebo recipients. Of the ≈30% of patients in either treatment group who withdrew from the study prematurely, significantly more dronedarone than placebo recipients withdrew because of adverse events (13% vs 8%; $p < 0.001$).[39]

• The incidence of diarrhoea, nausea, bradycardia, rash and QT interval prolongation in ATHENA was significantly higher in oral dronedarone than placebo recipients (figure 4). No significant between-group differences in the incidence of the other important treatment-emergent adverse events, such as pulmonary symptoms, interstitial lung disease and hyper-or hypothyroidism, were reported.[39]

• Elevations in serum creatinine levels were documented in significantly more dronedarone than placebo recipients in ATHENA (4.7% vs 1.3%; $p < 0.001$);[39] however, there was no significant between-group difference in serious elevations in serum creatinine levels (0.2% vs <0.1%). This may be due to the partial inhibition of tubular organic cation transporters (see section 2) rather than deteriorating renal function.[39] Abnormal liver function occurred with a similar frequency in the oral dronedarone 400 mg twice daily and placebo treatment groups in ATHENA (0.5% and 0.6% of patients).[39]

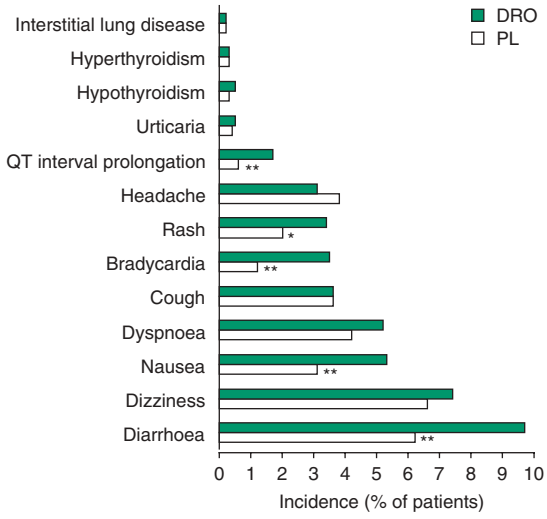


Fig. 4. Tolerability profile of oral dronedarone (DRO) in adult patients with atrial fibrillation or atrial flutter. Incidence of important (criteria not defined) treatment-emergent adverse events of any severity reported in the randomized, double-blind, placebo (PL)-controlled, parallel-group, multinational, phase III ATHENA study in which patients (mean age 72 years) received oral DRO 400 mg twice daily (n = 2291) or PL (n = 2313) for 30 months.[39] Data reported are for the modified intent-to-treat population. * $p < 0.01$, ** $p < 0.001$ vs DRO.

- There were no significant between-group differences in the incidence of serious adverse events, including gastrointestinal (3.5% vs 2.9% of patients), respiratory (1.8% vs 1.9%) and neurological (0.9% vs 1.2%) disorders, with dronedarone or placebo in ATHENA.[39]
- The incidence of serious cardiac-related adverse events with oral dronedarone in ATHENA was low (<1% of patients) and did not differ between oral dronedarone (0.7%) and placebo (0.6%).[39] *Torsade de pointes* was observed in one dronedarone recipient.[39]
- The adverse events profile of dronedarone in the ADONIS and EURIDIS[38] and ERATO[41] studies (in patients aged ≥21 years) was consistent with that in ATHENA.[39] There were no significant between-group differences with dronedarone or placebo therapy in the incidence of cardiac, dermatological, gastrointestinal, neurological or pulmonary adverse events in combined data from ADONIS and EURIDIS.[38]
- Hyperthyroidism (defined as free T3 or free T4 levels above the normal range, or thyrotropin levels below the normal range between the first administration of the study drug and 10 days past the last administration of the study drug) was less frequent in dronedarone than placebo recipients (8.4% vs 14.1%; $p < 0.005$), whereas the incidence of hypothyroidism (defined as free T3 or free T4 levels below the normal range or thyrotropin levels above the normal range between the first administration of the study drug and 10 days past the last administration of the study drug) did not significantly differ between dronedarone and placebo recipients (5.5% vs 3.5%).[38]
- No effect on the INR was observed in patients receiving concomitant oral anticoagulants in the ERATO study.[41] Although digoxin levels were slightly elevated, in patients receiving the drug concomitantly with dronedarone there was no significant difference between the proportions of dronedarone or placebo recipients with elevated digoxin levels that were outside the normal range (4.5% vs 2.8%).[41]
- The ANDROMEDA study in hospitalized patients with symptomatic heart failure and severe left ventricular systolic dysfunction was terminated early after review by an independent data and safety monitoring board because of tolerability issues.[44] Mortality rates of 8.1% (25 of 310 patients) and 3.8% (12 of 317) were observed in the dronedarone and placebo treatment groups during a median 2-month follow-up period (HR 2.13; 95% CI 1.07, 4.25; $p = 0.03$).[44] Worsening heart failure leading to death (3.2% of dronedarone and 0.6% of placebo recipients) was predominately responsible for the observed excess mortality rates.[44]

5. Dosage and Administration

Oral dronedarone is indicated to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent AF or atrial flutter, with a recent episode of AF/atrial flutter and associated cardiovascular risk factors (i.e. age >70 years, hypertension, diabetes mellitus, prior cerebrovascular accident, left atrial diameter ≥50 mm or LVEF

<40%) who are in sinus rhythm or who will be cardioverted.[8]

The recommended dosage of dronedarone is 400 mg twice daily, administered orally with the morning and evening meals.[8] Therapy with class II or III antiarrhythmics, such as amiodarone, disopyramide, dofetilide, flecainide, propafenone, quinidine and sotalol, and CYP3A inhibitors, such as ciclosporin (cyclosporin), clarithromycin, ketoconazole, nefazodone and ritonavir, must cease prior to the initiation of dronedarone therapy.[8]

Dosage adjustments are not required in elderly patients or those with renal or moderate hepatic impairment.[8] The efficacy and tolerability of dronedarone in children and adolescents aged <18 years have not been established.[8]

Based on the ANDROMEDA study,[44] dronedarone is contraindicated in patients with NYHA Class IV heart failure or those with NYHA Class II–III heart failure who have experienced a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic; this information features in a boxed warning in the US prescribing information.[8]

Caution, patient monitoring and/or dose adjustment is advised during the coadministration of dronedarone and other drugs including statins; sirolimus, tacrolimus and other CYP3A substrates with a narrow therapeutic range; β-blockers, selective serotonin reuptake inhibitors, tricyclic antidepressants and other CYP2D6 substrates; calcium channel antagonists; and warfarin.[8,35] Low doses of β-blockers or calcium channel antagonists should be administered initially with dronedarone, and the doses increased only after verification (via ECG) of tolerability.[8]

The local manufacturer's prescribing information should be consulted for detailed information, including other contraindications, drug interactions, monitoring requirements, precautions, and use in special patient populations.

6. Dronedarone: Current Status

Oral dronedarone has been approved in the US[8] and an application for the approval of oral dronedarone has been filed with the European Medicines Agency.[45]

In patients with AF and/or atrial flutter, oral dronedarone was more effective than placebo in reducing the risk of hospitalization or death, or of a documented recurrence of AF and/or atrial flutter in several well designed clinical studies. Oral dronedarone was also effective in terms of ventricular rate control and in reducing the time from randomization to a documented recurrence of AF. Oral dronedarone was generally well tolerated in these studies.

Acknowledgements and Disclosures

The manuscript was reviewed by: ***G.V. Naccarelli***, Division of Cardiology, Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania, USA; ***D.A. Sica***, Division of Nephrology, Virginia Commonwealth University, Richmond, Virginia, USA.

The preparation of this review was not supported by any external funding. During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article. Changes resulting from comments received were made on the basis of scientific and editorial merit.

References

1. Lip GY, Tse HF. Management of atrial fibrillation. Lancet 2007; 370 (9587): 604-18
2. Singh BN, Aliot E. Newer antiarrhythmic agents for maintaining sinus rhythm in atrial fibrillation: simplicity or complexity? Eur Heart J Suppls 2007; 9 Suppl. G: G17-25
3. Musco S, Conway EL, Kowey PR. Drug therapy for atrial fibrillation. Med Clin North Am 2008; 92 (1): 121-41
4. Brendorp B, Pedersen OD, Torp-Pedersen C, et al. A benefit-risk assessment of class III antiarrhythmic agents. Drug Saf 2002; 25 (12): 847-65
5. Tafreshi MJ, Rowles J. A review of the investigational antiarrhythmic agent dronedarone. J Cardiovasc Pharmacol Ther 2007 Mar; 12 (1): 15-26
6. Zimetbaum PJ. Dronedarone for atrial fibrillation: an odyssey. N Engl J Med 2009 Apr 30; 360 (18): 1811-3
7. Lombardi F, Terranova P. Pharmacological treatment of atrial fibrillation: mechanisms of action and efficacy of class III drugs. Curr Med Chem 2006; 13 (14): 1635-53
8. sanofi-aventis. MULTAQ (dronedarone) tablets: prescribing information [online]. Available from URL: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022425lbl.pdf [Accessed 2009 Jul 8]
9. Sun W, Chen F, Esmailian F, et al. Acute effects of dronedarone on the potassium currents in human atrial cells. J Am Coll Cardiol 2002 Mar 6; 39 Suppl. A: 105

10. Gautier P, Guillemare E, Marion A, et al. Electrophysiologic characterization of dronedarone in guinea pig ventricular cells. J Cardiovasc Pharmacol 2003 Feb; 41 (2): 191-202
11. Guillemare E, Marion A, Nisato D, et al. Inhibitory effects of dronedarone on muscarinic K^+ current in guinea pig atrial cells. J Cardiovasc Pharmacol 2000 Dec; 36 (6): 802-5
12. Altomare C, Barbuti A, Viscomi C, et al. Effects of dronedarone on acetylcholine-activated current in rabbit SAN cells. Br J Pharmacol 2000 Jul; 130 (6): 1315-20
13. Thomas D, Kathofer S, Zhang W, et al. Acute effects of dronedarone on both components of the cardiac delayed rectifier K^+ current, HERG and KvLQT1/minK potassium channels. Br J Pharmacol 2003 Nov; 140 (5): 996-1002
14. Lalevée N, Barrère-lemaire S, Gautier P, et al. Effects of amiodarone and dronedarone on voltage-dependent sodium current in human cardiomyocytes. J Cardiovasc Electrophysiol 2003 Aug; 14 (8): 885-90
15. Watanabe Y, Kimura J. Acute inhibitory effect of dronedarone, a noniodinated benzofuran analogue of amiodarone, on Na+/Ca2+ exchange current in guinea pig cardiac ventricular myocytes. Naunyn Schmiedebergs Arch Pharmacol 2008 Jun; 377 (4-6): 371-6
16. Hodeige D, Heyndrickx JP, Chatelain P, et al. SR 33589, a new amiodarone-like antiarrhythmic agent: anti-adrenoceptor activity in anaesthetized and conscious dogs. Eur J Pharmacol 1995 Jun 6; 279: 25-32
17. Djandjighian L, Planchenault J, Finance O, et al. Hemodynamic and antiadrenergic effects of dronedarone and amiodarone in animals with a healed myocardial infarction. J Cardiovasc Pharmacol 2000 Sep; 36: 376-83
18. Sun W, Sarma JS, Singh BN. Chronic and acute effects of dronedarone on the action potential of rabbit atrial muscle preparations: comparison with amiodarone. J Cardiovasc Pharmacol 2002 May; 39 (5): 677-84
19. Sun W, Sarma JS, Singh BN. Electrophysiological effects of dronedarone (SR33589), a noniodinated benzofuran derivative, in the rabbit heart: comparison with amiodarone. Circulation 1999 Nov 30; 100 (22): 2276-81
20. Manning A, Thisse V, Hodeige D, et al. SR 33589, a new amiodarone-like antiarrhythmic agent: electrophysiological effects in anesthetized dogs. J Cardiovasc Pharmacol 1995 Feb; 25 (2): 252-61
21. Moro S, Ferreiro M, Celestino D, et al. In vitro effects of acute amiodarone and dronedarone on epicardial, endocardial, and M cells of the canine ventricle. J Cardiovasc Pharmacol Ther 2007 Dec; 12 (4): 314-21
22. Varro A, Takacs J, Nemeth M, et al. Electrophysiological effects of dronedarone (SR 33589), a noniodinated amiodarone derivative in the canine heart: comparison with amiodarone. Br J Pharmacol 2001 Jul; 133 (5): 625-34
23. Celestino D, Medei E, Moro S, et al. Acute in vitro effects of dronedarone, an iodine-free derivative, and amiodarone, on the rabbit sinoatrial node automaticity: a comparative study. J Cardiovasc Pharmacol Ther 2007 Sep; 12 (3): 248-57
24. Aimond F, Beck L, Gautier P, et al. Cellular and in vivo electrophysiological effects of dronedarone in normal and postmyocardial infarcted rats. J Pharmacol Exp Ther 2000 Jan; 292: 415-24
25. Manning AS, Bruyninckx C, Ramboux J, et al. SR 33589, a new amiodarone-like agent: effect on ischemia- and reperfusion-induced arrhythmias in anesthetized rats. J Cardiovasc Pharmacol 1995 Sep; 26: 453-61
26. Rochetaing A, Barbe C, Kreher P. Beneficial effects of amiodarone and dronedarone (SR 33589b), when applied during low-flow ischemia, on arrhythmia and functional parameters asssessed during reperfusion in isolated rat hearts. J Cardiovasc Pharmacol 2001 Oct; 38 (4): 500-11
27. Verduyn SC, Vos MA, Leunissen HDM, et al. Evaluation of the acute electrophysiologic effects of intravenous dronedarone, an amiodarone-like agent, with special emphasis on ventricular repolarization and acquired torsade de pointes arrhythmias. J Cardiovasc Pharmacol 1999 Feb; 33: 212-22
28. Verduyn SC, Leunissen JD, Vos MA. Intravenous administration of an amiodarone like agent, dronedarone (SR33589), does not evoke but suppresses torsade de pointes arrhythmias. Circulation 1996 Oct 15; 94 (8 Suppl.): 745
29. Finance O, Manning A, Chatelain P. Effects of a new amiodarone-like agent, SR 33589, in comparison to amiodarone, D,L-sotalol, and lignocaine, on ischemia-induced ventricular arrhythmias in anesthetized pigs. J Cardiovasc Pharmacol 1995 Oct; 26: 570-6
30. Guiraudou P, Pucheu SC, Gayraud R, et al. Involvement of nitric oxide in amiodarone- and dronedarone-induced coronary vasodilation in guinea pig heart. Eur J Pharmacol 2004 Aug 2; 496 (1-3): 119-27
31. Pantos C, Mourouzis I, Delbruyere M, et al. Effects of dronedarone and amiodarone on plasma thyroid hormones and on the basal and postischemic performance of the isolated rat heart. Eur J Pharmacol 2002 May 31; 444: 191-6
32. Stoykov I, van Beeren HC, Moorman AF, et al. Effect of amiodarone and dronedarone administration in rats on thyroid hormone-dependent gene expression in different cardiac components. Eur J Endocrinol 2007 Jun; 156 (6): 695-702
33. Wadhani N, Sarma JSM, Singh BN, et al. Dose-dependent effects of oral dronedarone on the circadian variation of RR and QT intervals in healthy subjects: implications for antiarrhythmic actions. J Cardiovasc Pharmacol Ther 2006 Sep 1; 11 (3): 184-90
34. Tschuppert Y, Buclin T, Rothuizen LE, et al. Effect of dronedarone on renal function in healthy subjects. Br J Clin Pharmacol 2007 Dec; 64 (6): 785-91
35. sanofi-aventis. US FDA Cardiovascular & Renal Drugs Advisory Committee: briefing material for dronedarone [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4417b1-01-FDA.pdf [Accessed 2009 Jun 3]
36. Touboul P, Brugada J, Capucci A, et al. Dronedarone for prevention of atrial fibrillation: a dose-ranging study. Eur Heart J 2003 Aug; 24 (16): 1481-7
37. Damy T, Pousset F, Caplain H, et al. Pharmacokinetic and pharmacodynamic interactions between metoprolol and dronedarone in extensive and poor CYP2D6 metabolizers healthy subjects. Fundam Clin Pharmacol 2004 Feb; 18 (1): 113-23
38. Singh BN, Connolly SJ, Crijns HJ, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med 2007 Sep 6; 357 (10): 987-99
39. Hohnloser SH, Crijns HJ, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009 Feb 12; 360 (7): 668-78
40. Hohnloser SH, Connolly SJ, Crijns HJ, et al. Rationale and design of 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. J Cardiovasc Electrophysiol 2008 Jan; 19 (1): 69-73

41. Davy JM, Herold M, Hoglund C, 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 Sep; 156 (3): 527.e1-9
42. Hohnloser SH, Connolly SJ, Crijins HJ, et al. Effects of dronedarone on clinical outcomes in patients with atrial fibrillation and congestive heart failure: insights from ATHENA [abstract]. Heart Rhythm Society's 30th Annual Scientific Sessions; 2009 May 13-16; Boston (MA)
43. Hohnloser SH, Connolly SJ, van Eickels M, et al. Effect of dronedarone on cardiovascular outcomes: a meta-analysis of five randomized controlled trials in 6157 patients with atrial fibrillation/flutter [abstract no. 1020-54]. J Am Coll Cardiol 2009; 53 (10 Suppl. A): A113-4
44. Køber L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008 Jun 19; 358 (25): 2678-87
45. sanofi-aventis. FDA approved Multaq® for patients with atrial fibrillation or atrial flutter [online]. Available from URL: http://en.sanofi-aventis.com/binaries/20090702_multaq_en_tcm28-25557.pdf [Accessed 2009 Jul 10]

Correspondence: *Sheridan M. Hoy*, Wolters Kluwer Health | Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand. E-mail: demail@adis.co.nz