Review article

Dronedarone—current status in management of atrial fibrillation

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KEYWORDS

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ABSTRACT

Atrial fibrillation (AF) is the most common of the serious cardiac rhythm disturbances and is responsible for substantial morbidity and mortality. Available drug therapy for AF has modest efficacy and is associated with the risk of life-threatening pro-arrhythmic complications.

Dronedarone is a newer therapeutic agent with a structural resemblance to amiodarone and a better side effect profile. It is a multichannel blocker with antiadrenergic properties and has been evaluated in both rate and rhythm control strategies in the management of AF. In this review, we discuss the current role of dronedarone in the contemporary management of AF.

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Introduction

Atrial fibrillation (AF) is a common arrhythmia in clinical practice contributing to significant cardiovascular morbidity and mortality. The prevalence of AF increases with age and adversely impacts the healthcare resources. Major trials have shown the adequacy of rate-control in the management of AF, nevertheless the achievement of sustained sinus rhythm has been shown to improve quality of life and exercise performance.¹ Current antiarrhythmic agents employed in the treatment of AF are limited by their modest efficacy, pro-arrhythmic effects, and long-term toxicity.^{2–5} Dronedarone is a new antiarrhythmic agent which has been evaluated in many multicentre trials (Table 1).

Dronedarone

Dronedarone is a newer benzofuran derivative having a structural resemblance to amiodarone with two important molecular changes: it lacks the iodine moiety responsible for thyroid dysfunction and it has a methane sulfonyl group that decreases lipophilicity, resulting in a shorter half-life leading to

lower tissue accumulation and less long-term toxicity. It is an orally administered drug cleared by non-renal mechanism and a steady-state serum level is achieved in 5–7 days. The bioavailability is relatively low (15%) because of extensive hepatic first-pass metabolism by cytochrome P450 (CYP) 3A4 and CYP2D6, thus requiring twice daily dosing to achieve steady-state serum levels.⁶ Dronedarone is a multichannel blocker with electrophysiological properties similar to those of amiodarone. It decreases slowly activating delayed-rectifier K⁺ current I (Kr), and inward rectifier potassium current I (K1), L-type Ca²⁺ current I (Ca [L]) and maximum rate of rise of action potential (dV/dt max) with a concentration and frequency-dependent relationship (I [Na]).^{7,8} The drug has very little effect on the QT interval, and proarrhythmia has not been observed. In vitro studies have shown a more efficient inhibition of (I [Na]) in atrial myocytes compared to amiodarone showing atrial selective antiarrhythmic properties.^{7,9} Dronedarone is an approximately 100 times more potent inhibitor on muscarinic acetylcholine receptor-operated K⁺ current IK (ACh) than amiodarone. This property may be involved, at least in part, in its antiarrhythmic action against AF, as vagal activation is known to play a role in the pathophysiology of AF. Like amiodarone, dronedarone can partially inhibit the effects of stimulation of the beta 2 and alpha adrenoceptor system that may play a pivotal role in the onset of severe ventricular rhythm disturbances.¹⁰

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Table 1
Summary of trials on dronedarone.

	Inclusion criteria	Follow-up	Patients	Primary end points	Outcomes
DAFNE ²⁰	Persistent AF	6 mo	270	Time to AF recurrence	Time to AF recurrence increased on dronedarone 800 mg, with a median of 60 days versus 5.3 days in the placebo group ($P=0.001$)
EURIDIS/ ADONIS ¹¹	Paroxysmal AF	12 mo	615/629	Time to AF recurrence	At 12 months the recurrence of AF/AFL was 64.1% with dronedarone versus 75.2% with placebo ($P<0.001$). Median time to AF recurrence prolonged from 53 days to 116 days
ERATO ¹³	Permanent AF	6 mo	174	Mean ventricular rate on day 14	Reduction of 11.7 bpm in ventricular rate at day 14. This effect was sustained for 6 months
ANDROMEDA ¹⁶	NYHA Class III–IV CHF with LVEF <35%	2 mo	627	All-cause mortality or admission from worsening CHF	Trial was prematurely terminated due to excess mortality secondary to the worsening of HF in dronedarone group (HR=2.13)
ATHENA ¹²	Paroxysmal or persistent AF or flutter, +age ≥ 70 years + one or more risk factors	21 mo	4628	Death from all causes and hospitalisation for the 1st cardiovascular event	Primary outcome was 31.9% in dronedarone group versus 39.4% in placebo group (HR=0.76, 0.84; $P<0.001$)
PALLAS ¹⁴	Permanent AF and additional risk factors	3.5 mo	10,800	1. Composite end point of stroke, myocardial infarction, systemic embolism or death from cardiovascular causes 2. Unplanned hospitalisation for a cardiovascular cause or death	Primary end point in 8.2% versus 3.6/100 pt years; HR=2.29. Secondary end point in 25.3 versus 12.9/100 pt years. HR=1.95 Cardiovascular hospitalisations 22.5 versus 11.4/100 pt years. HR=1.97e

AF: atrial fibrillation, AFL: atrial flutter, CHF: congestive heart failure, HF: heart failure, HR: hazard ratio, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association.

Dronedarone in paroxysmal and persistent atrial fibrillation

The first of the studies to evaluate the effectiveness of dronedarone in rhythm control was the EURIDIS and ADONIS trials which were placebo-controlled and identical in design, conducted in European, and non-European centres (USA, Argentina, Canada, South Africa, and Australia), respectively.¹¹ Both these pivotal trials aimed at assessing the efficacy of dronedarone in the maintenance of normal sinus rhythm after electrical, pharmacological, or spontaneous conversion of paroxysmal AF or atrial flutter (AFL). It was shown that dronedarone reduced the 1 year symptomatic recurrences (77.5% vs 67.1% in the European trial; 72.8% vs 61.1% in the non-European trial) and prolonged the median time to recurrence (41–96 days in the European trial; 59–158 days in the non-European trial). Further, in both the trials, when the recurrence occurred, the mean ventricular rates were much slower compared to placebo (117 beats/min [bpm] vs 102 bpm and 116 bpm vs 104 bpm, respectively). In the period of 1 year, toxic effects related to lung, thyroid and liver were not significantly increased in the dronedarone group. Though, not an intended end point of the study, post hoc analysis showed a decrease in the combined outcome of hospitalisation and mortality. This observation led to the design of the ATHENA trial to evaluate the effect of treatment on all-cause mortality and morbidity in patients with paroxysmal and persistent AF or AFL.¹² It was a prospective, randomised, placebo-controlled, double-blind, trial evaluating the effects of dronedarone versus placebo (ratio 1:1)

in patients with paroxysmal or persistent AF/AFL who had additional risk factors like hypertension, diabetes, age >70 years, previous stroke or transient ischaemic attack (TIA), systemic embolism, and left ventricle (LV) dysfunction. This was the largest trial assessing efficacy of an anti-arrhythmic drug in AF population in reduction of cardiovascular outcomes. In the treatment arm, there was a significant reduction in hospitalisations related to cardiovascular events (36.9% vs 29.3%) particularly due to reduction in hospital admissions for AF. There was, however, no benefit in hospitalisations due to heart failure (HF), ventricular arrhythmias and non-fatal cardiac arrest. Numerically there were fewer deaths in the dronedarone arm compared to placebo (139 vs 116). Overall, there was 30% reduction in cardiovascular deaths and 45% decrease in arrhythmia-related deaths. ATHENA specifically excluded patients who had either haemodynamic instability or severe (New York Heart Association [NYHA] Class IV) HF. An interesting observation in this trial was that there was lesser number of ischaemic strokes with the drug though the frequency of haemorrhagic strokes was similar. This decrease in strokes was particularly impressive in those with ≥ 2 CHADS₂ score.

Dronedarone in permanent atrial fibrillation

Achievement of adequately controlled ventricular rates is the principal objective in the management of permanent AF. The possibility that dronedarone could have rate-control properties was suggested by the fact that patients in EURIDIS and

ADONIS trials who suffered recurrences had lower ventricular rates compared to placebo. ERATO trial specifically assessed the efficacy of dronedarone in the control of ventricular rate in patients with permanent AF, when added to standard rate-control therapy which included beta-blockers, calcium antagonists, and digoxin.¹³ In this prospective study, 174 elderly patients with permanent AF were randomised to treatment for 6 months with dronedarone ($n=85$), or matching placebo ($n=89$). The change in the mean ventricular rate between baseline and day 14 was objectively documented by 24-hour Holter. In addition, ventricular rate was also assessed during sub-maximal and maximal exercise.

Dronedarone achieved a significant decrease in the mean 24-hour ventricular rate at 14 days (11.7 bpm, $P<0.0001$) which was sustained at 6 months. During maximal exercise compared to placebo, there was a mean reduction of 24.5 bpm ($P<0.0001$), without any compromise in exercise tolerance. The effects of dronedarone were not influenced but were additive to other rate-control agents used in the study. Results of the ATHENA trial showed that the benefit of improved cardiovascular outcomes with dronedarone was also perceived in the subset of patients who progressed to permanent AF. This indicated that the benefits of dronedarone possibly extended beyond those that were obtained by rhythm control alone. The PALLAS was an ambitious study intending to demonstrate this hypothesis in patients with permanent AF having additional cardiovascular risk factors.¹⁴ This trial was terminated for safety reasons 1 year after enrolment commenced achieving a mean follow-up of just 3.5 months. There was a highly significant increase in strokes, hospitalisations, and mortality related to cardiovascular causes in the dronedarone arm. There was an increase in HF-related hospitalisations and mortality. Surprisingly, in contrast to ATHENA study, there was a three-fold increase in arrhythmic deaths contributing to the cardiovascular mortality. The PALLAS generated a very sound evidence of harmful effects of dronedarone in permanent AF patients with cardiovascular risk factors.

Dronedarone in heart failure

Amiodarone is a popular anti-arrhythmic agent in clinical practice used frequently for suppression of atrial and ventricular arrhythmias in patients with HF; it has however not shown survival benefit in this population. The inability of amiodarone to reduce mortality in this vulnerable subset was attributed to its pro-arrhythmic effects.¹⁵ Similar lack of mortality benefit was seen with sotalol. As dronedarone was known to be a drug with electrophysiological properties similar to amiodarone and being devoid of its side effects, it was hypothesised that it would show mortality benefit in HF patients. In the ATHENA study, in the dronedarone group, stable HF patients with LV dysfunction did as well as those with preserved LV function. The ANDROMEDA trial was a multicentre, double-blind, parallel-group, placebo-controlled study designed on the background of these facts to evaluate the effect of dronedarone on reduction in hospitalisations for worsening HF or death, in a high-risk population of patients with recently

decompensated congestive heart failure (CHF).¹⁶ This study did not require patients to have AF.

After inclusion of 627 patients (310 in the dronedarone group and 317 in the placebo group), the trial was prematurely terminated for safety reasons. During a median follow-up of 2 months, 25 patients in the dronedarone group (8.1%) and 12 patients in the placebo group (3.8%) died (hazard ratio in the dronedarone group, 2.13; 95% confidence interval [CI], 1.07–4.25; $P=0.03$). The excess mortality was predominantly related to worsening of HF—10 deaths in the dronedarone group and two in the placebo group. The primary end point which was the composite of death from any cause or hospitalisation for HF did not differ significantly between the two groups; there were 53 events in the dronedarone group (17.1%) and 40 events in the placebo group (12.6%) (hazard ratio, 1.38; 95% CI, 0.92–2.09; $P=0.12$). It was concluded from this study that in patients with severe HF and LV systolic dysfunction, treatment with dronedarone was associated with increased early mortality related to the worsening of HF.

Dronedarone versus amiodarone

Historically, amiodarone has been the most effective anti-arrhythmic agent in maintaining sinus rhythm in patients with AF and has been shown to be superior to sotalol and propafenone as a rhythm control agent.¹⁷ Its usage has been limited due to its cumulative and frequently irreversible toxicity. Dronedarone is an amiodarone congener with similar electrophysiological properties without the toxic and pro-arrhythmic effects. There exist some important differences between the two drugs. Amiodarone has a slow onset of action and requires 1–3 weeks to achieve therapeutic response and has a long half-life of 40–55 days. In contrast, dronedarone has a half-life of 13–19 hours and reaches a steady-state plasma concentration in 4–8 days.¹⁸

The relative effectiveness of amiodarone and dronedarone achieving rhythm control in 504 patients with persistent AF was assessed by DIONYSOS trial.¹⁹ Patients were included if they had a need for cardioversion and needed to be on anti-arrhythmic drugs. They were randomised to receive amiodarone 600 mg once daily for 28 days followed by 200 mg once daily or 400 mg twice daily of dronedarone with median treatment duration of 7 months. The rate of AF recurrence was higher in the dronedarone group (63.5% vs 42%, $P<0.0001$). The rate of discontinuation of the drug due to intolerance was lower with dronedarone (10% vs 13.3%) and so was the frequency of thyroid disorders (1.2% vs 7.8%). Discontinuation of dronedarone was predominantly due to gastrointestinal side effects. Dronedarone thus was shown to be less effective than amiodarone in maintaining sinus rhythm but demonstrated to have better safety profile.

Choice of dosage

The evidence for appropriate therapeutic dosage of dronedarone (800 mg daily) is derived solely from the DAFNE study

which was designed to compare three different doses of this drug with placebo for the maintenance of sinus rhythm following electrical cardioversion in patients with AF.²⁰ The primary objective was to assess the efficacy of several doses of dronedarone for the maintenance of sinus rhythm for 6 months in patients undergoing cardioversion for AF.

Patients fulfilling the entry criteria for the study were randomly assigned to either 400mg twice daily, 600mg twice daily, 800mg twice daily or placebo, which were continued for 6 months. The primary end point was the time to first recurrence of AF after conversion to sinus rhythm. Secondary study endpoints were spontaneous conversion of AF following randomisation, heart rate in case of AF recurrence and the incidence of side effects.

Within a 6-month follow-up, the time to AF relapse increased on dronedarone 800mg, with a median of 60 days versus 5.3 days in the placebo group (relative risk reduction 55% [95% CI, 28–72%] $P=0.001$). No significant effect was seen at higher doses. Spontaneous conversion to sinus rhythm on dronedarone occurred in 5.8–14.8% of patients ($P=0.026$). There were no pro-arrhythmic reactions. Drug-induced QT prolongation was only noticed in the 1600mg group. Premature drug discontinuations affected 22.6% of subjects given 1600mg dronedarone versus 3.9% on 800mg and were mainly due to gastrointestinal side effects. No evidence of thyroid, ocular or pulmonary toxicity was found. Thus, dronedarone, at 800mg daily dose appears to be effective and safe for the prevention of AF relapses after cardioversion.

We, however, have no data on the lower doses of the drug particularly to assess if the safety profile improves in permanent AF patients. The HARMONY is a new pacemaker-patient-based trial to examine the efficacy and safety of a low dose of 150–225mg of dronedarone with 750mg ranolazine on AF burden. About 150 patients will be enrolled at 45 sites in North America and Europe, starting January 2012.

Dronedarone—present status in atrial fibrillation management

The data generated by clinical experience with dronedarone clearly demonstrates that our quest for an ideal anti-arrhythmic agent suitable for all subsets of AF population is far from complete. Advantages in favour of this new antiarrhythmic drug are ease of initiation with a single dose as an outpatient, decreased requirement for monitoring end organ toxicity and no significant interaction with warfarin. Post drug initiation surveillance is limited to periodic electrocardiograms and liver function tests due to reports of rare hepatocellular injury.²¹ Though, less effective than amiodarone in the prevention of AF, it is comparatively safer and well tolerated in patients with preserved LV function. In paroxysmal and persistent AF/AFL it has been associated with decreased hospitalisations and cardiovascular mortality driven by its favourable effect on AF. This evidence from ATHENA, the largest anti-arrhythmic drug trial in AF, resulted in approval by the Federal Drug Administration in the USA and incorporation into the European and American guidelines for this indication.^{22,23} In patients with

advanced HF and with severely impaired ventricular dysfunction, use of dronedarone increased mortality due to worsening HF and patients with permanent AF/AFL with risk factors for vascular events had increased rates of stroke, HF, and cardiovascular deaths. Similarly, outcomes are poor in patients with permanent AF and risk factors for vascular disease. Clearly, this drug is harmful in these groups of patients and should not be used. In AF patients who require amiodarone but have experienced drug toxicity, dronedarone provides a useful substitution.

References

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22:983–8.
2. Nattel S, Carlsson L. Innovative approaches to anti-arrhythmic drug therapy. *Nat Rev Drug Discov* 2006;5:1034–49.
3. Nattel S, Opie LH. Controversies in atrial fibrillation. *Lancet* 2006;367:262–72.
4. Riley MJ, Marrouche NF. Ablation of atrial fibrillation. *Curr Probl Cardiol* 2006;31:361–90.
5. Singh BN, Singh SN, Reda DJ, et al. Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) Investigators. Amiodarone versus sotalol for atrial fibrillation. *N Engl J Med* 2005;352:1861–72.
6. Han TS, Williams GR, Vanderpump MP. Benzofuran derivatives and the thyroid. *Clin Endocrinol (Oxford)* 2009;70:2–13.
7. Gautier P, Guillemare E, Marion A, et al. Electrophysiologic characterization of dronedarone in guinea pig ventricular cells. *J Cardiovasc Pharmacol* 2003;41:191–202.
8. Varró A, Takács J, Németh M, et al. Electrophysiological effects of dronedarone (SR 33589), a noniodinated amiodarone derivative in the canine heart: comparison with amiodarone. *B J Pharmacol* 2001;133:625–34.
9. Lalevéé N, Nargeot J, Barrère-Lemaire S, et al. Effects of amiodarone and dronedarone on voltage-dependent sodium current in human cardiomyocytes. *J Cardiovasc Electrophysiol* 2003;14:885–90.
10. 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;279:25–32.
11. Singh BN, Connolly SJ, Crijns HJ, et al. For the EURIDIS and ADONIS investigators. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007;357:987–99.
12. Hohnloser SH, Crijns HJGM, Martin van Eickels, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009;360:668–78.
13. Davy JM, Herold M, Høglund 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;156:527e1–9.
14. Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in high risk atrial fibrillation. For the PALLAS investigators. *N Engl J Med* 2011;365:2268–76.
15. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225–37.
16. Køber L, Torp-Pedersen C, McMurray JJ, et al. Dronedarone study group increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008;358:2678–87.
17. Roy D, Talajic M, Dorian P, et al. Amiodarone to prevent recurrence of atrial fibrillation. *N Engl J Med* 2000;342:913–20.
18. McEvoy GK, ed. Amiodarone hydrochloride. In: *AHFS Drug Information 2010*. Bethesda, MD: American Society of Health-System Pharmacists 2010:1671–85.

19. Le Heuzey JY, De Ferrari GM, Radzik D, et al. A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: the DIONYSOS study. *J Cardiovasc Electrophysiol* 2010;21:597–605.
20. Touboul P, Brugada J, Capucci A, et al. Dronedarone for prevention of atrial fibrillation: a dose-ranging study. *Eur Heart J* 2003;24:1481–7.
21. FDA Drug Safety Communication: severe liver injury associated with the use of dronedarone (marketed as Multaq). <http://www.fda.gov/Drugs/DrugSafety/ucm240011.htm>.
22. ESC Guidelines for the management of atrial fibrillation. *Eur Heart J* 2010;31:2369–429.
23. Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS Focused Update on the Management of Patients with Atrial Fibrillation. *J Am Coll Cardiol* 2011;57:223–42.