# Dronedarone

**Dr Zhuo Min Chong**
MRCP, Core Medical Trainee, Monklands Hospital, Airdrie, UK

**Dr Thekkepat Sandeep**
FRCP, Consultant Physician, Monklands Hospital, Airdrie, UK

**Correspondence to:**
Dr Thekkepat Sandeep, David Mathews Diabetes Centre, Monklands Hospital, Monkscourt Avenue, Airdrie ML6 0JS, UK; email: Thekkepat.Sandeep@lanarkshire.scot.nhs.uk

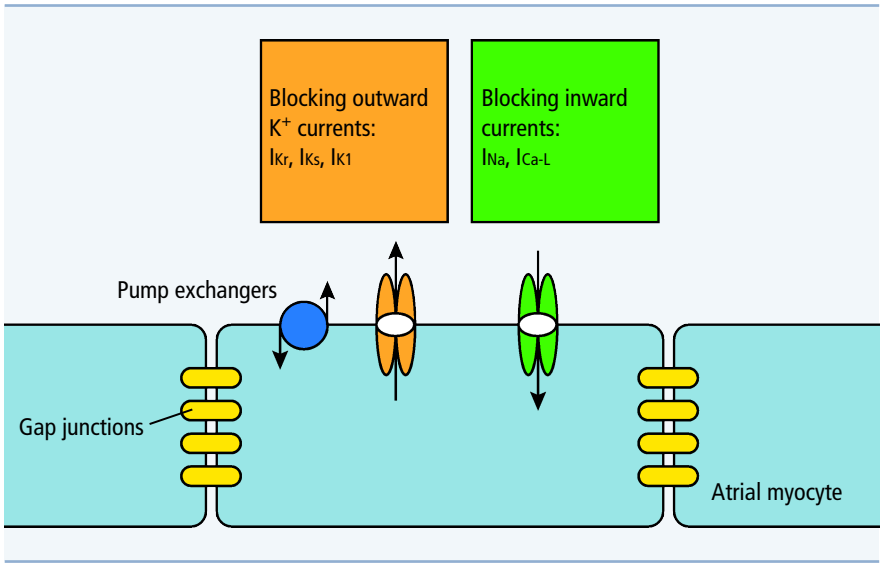


**Figure 1.** Pharmacological action of dronedarone in an atrial myocyte

## Introduction

Atrial fibrillation is the most common arrhythmia worldwide. It often occurs concurrently with heart disease, which has a higher prevalence in the diabetic population. Amiodarone is used in both stable and unstable atrial fibrillation, but its lung and thyroid toxicity makes it unsuitable for long-term use. Dronedarone is a non-iodinated congener of amiodarone. It is hoped to have no iodine-related side effects, so potentially better tolerance in a wider patient group.

## Pharmacology

Dronedarone, like its congener amiodarone, works by blocking potassium ($I_{Kr}$, $I_{Ks}$, $I_{K1}$), sodium ($I_{Na}$) and slow L-type calcium ($I_{Ca\text{-}L}$) transmembrane channels to control rhythm (Figure 1); and anti-adrenergic properties to control rate. Dronedarone non-competitively blocks α- and β-adrenoreceptors. It reduces vagal activation by inhibiting the muscarinic acetylcholine receptor-operated potassium channel, possibly reducing the recurrence of atrial fibrillation.

Dronedarone is a benzofuran, electropharmacologically similar to amiodarone but with one main structural difference. The iodine molecule contained in amiodarone has been substituted by a methane-sulphonyl group. This confers its main differences from amiodarone in terms of its bioavailability, half-life and most importantly iodine-related side effects. The methane-sulphonyl group decreases dronedarone's lipophilicity, shortening its half-life to 24 hours (*cf.* amiodarone 50 days), hence reducing levels of tissue accumulation. Dronedarone's absolute bioavailability is approximately 15% due to significant first pass metabolism. It is highly bound to plasma proteins, metabolised by the CYP3A4 system in the liver and excreted faecally.

The adverse side effect profile of dronedarone is extrapolated from amiodarone as no long-term toxicity data are available as yet. The ANDROMEDA study (the Anti-arrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease) has shown a two-fold increase in mortality from heart failure if dronedarone is administered to patients with New York Heart Association (NYHA) class IV and decompensated NYHA class II/III.[1] Liver toxicity has also been reported and, as few data are available, dronedarone is contraindicated in patients with hepatic impairment. As dronedarone inhibits CYP3A4, concomitant use of antifungals, macrolides and protease inhibitors is contraindicated. As a CYP2D6 inhibitor, dose adjustments

of concomitant metoprolol will be necessary. During various trials, an increase in creatinine not thought to be related to renal function has also been noted. Due to the absence of iodine molecule and lack of tissue accumulation, it is hypothesised that toxic side effects from amiodarone, such as thyroid dysfunction and pulmonary fibrosis, should be minimal.

## Trials of safety and efficacy

Three large studies have looked at the safety and efficacy of dronedarone as monotherapy or add-on therapy. The studied dose of dronedarone was 400mg twice daily in all three trials.

The ATHENA study (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400mg BID for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter) was the first large multicentre, double-blind study comparing dronedarone to placebo in patients with atrial fibrillation and cardiovascular risk factors, such as age >70 years, hypertension, diabetes mellitus, cerebrovascular disease, left ventricular dysfunction and left atrial dilatation.[2] A total of 4628 patients were randomised into the dronedarone arm and the placebo arm. The dronedarone group was found to have a reduced incidence of hospitalisation from cardiovascular events or death (hazard ratio [HR] 0.76; 95% confidence interval [CI] 0.69–0.84; p<0.001). Additionally, the study demonstrated that dronedarone maintained sinus rhythm at twice the duration of placebo (116 days *cf.* 53 days) and reduced ventricular rate during recurrence. These were postulated to be the reasons why dronedarone conferred benefit. The limitation in ATHENA is that it excluded patients with permanent atrial fibrillation and patients with severe or decompensated heart failure; both potential patient groups who may benefit from dronedarone.

A large (n=3236), multicentre, double-blind, randomised trial named PALLAS (Permanent Atrial fibriLLAtion Study) investigated the effects of dronedarone on hospitalisation due to major vascular events or death.[3] Unfortunately, it was stopped for safety reasons after a year as the dronedarone arm's cardiovascular mortality rate was double that of the placebo arm (HR 2.11; 95% CI 1.00–4.49; p=0.046). Similarly, the rate of hospitalisation due to major vascular events in the dronedarone arm was double that of the placebo arm (HR 1.97; 95% CI 1.44–2.70; p<0.001). Importantly, the deaths due to arrhythmias were increased, a finding that is inconsistent with the ATHENA study. The early termination of PALLAS reduced its statistical power; however, its findings are consistent with an earlier study, ANDROMEDA.

ANDROMEDA, a randomised, double-blind, placebo-controlled study,[1] investigated the effect of dronedarone on patients with decompensated heart failure and patients with NYHA class III/IV. It had a total of 627 patients, with 310 randomised to the dronedarone group. Similar incidences of the study's primary endpoint, hospitalisation for heart failure or death, were noted in both groups, but the mortality rate of dronedarone was more than twice that of placebo (HR 2.13; 95% CI 1.07–4.25; p=0.03). This difference was attributed to worsening heart failure in the dronedarone group.

As a result of the latter two studies, the European Society of Cardiology now recommends that dronedarone should not be used for patients with permanent atrial fibrillation and patients with severe or decompensated heart failure.[4]

## Specific evidence for use in diabetes

Diabetes has been identified as one of the cardiovascular risk factors in atrial fibrillation. As a result, all three large studies have included a proportion of diabetic patients. Approximately 35% of patients in PALLAS and 20% of patients in the ANDROMEDA study had diabetes. They were divided equally across both arms, but no subgroup analysis has been undertaken. Unfortunately, the number of patients with diabetes was not declared in the ATHENA study. There are no specific studies to date looking at the effects of dronedarone in diabetic patients.

## Discussion

Dronedarone has been marketed to be electrophysiologically similar to amiodarone, without the long-term toxicity. It has initially shown much promise of reducing cardiovascular mortality and morbidity by reducing the frequency of atrial fibrillation recurrence and lowering heart rate. Further studies have shown that dronedarone may be harmful to patients who have severe or decompensated heart failure or permanent atrial fibrillation. The reason behind this is not yet clear, but it has been postulated that worsening heart failure and pro-arrhythmic tendencies may be the main drivers of harm caused by dronedarone. More studies need to be conducted to understand the effects of dronedarone in patients with heart failure and permanent atrial fibrillation. It is a very promising drug and its potential for benefit may be great, especially in unstable patients to avoid the toxicities related to amiodarone. However, this is the same category of patients where an alarming rate of harm has been noted.

### Key points

- Dronedarone is a non-iodinated congener of amiodarone without the associated pulmonary and thyroid side effects
- The ATHENA trial has shown that dronedarone has rhythm- and rate-controlling benefits
- Dronedarone is not recommended for use in patients with severe or decompensated heart failure or permanent atrial fibrillation, but the pathophysiology behind this will require further investigation

## Acknowledgements

Many thanks to Professor Miles Fisher for his support with the article.

## Declaration of interests

There are no conflicts of interest.

## References

1. Kober L, *et al.* Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008;358:2678–87.
2. Hohnloser S, *et al.* Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009;260:668–78.
3. Connolly S, *et al.* Dronedarone in high-risk permanent atrial fibrillation. *N Engl J Med* 2011; 10.1056/NEJMOa1109867.
4. Bax J, Camm J. European Society of Cardiology Atrial Fibrillation Guidelines. Dronedarone and the PALLAS Trial Results. www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/Dronedarone_Pallas_Trial_Results_%20Aug_2011.pdf [accessed 18/12/2011].

# Drug notes

**Dronedarone**