EXPERT REVIEW

# Safety and Efficacy of Dronedarone in the Treatment of Atrial Fibrillation/Flutter

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**Abstract:** Dronedarone is an amiodarone analog but differs structurally from amiodarone in that the iodine moiety was removed and a methane-sulfonyl group was added. These modifications reduced thyroid and other end-organ adverse effects and makes dronedarone less lipophilic, shortening its half-life. Dronedarone has been shown to prevent atrial fibrillation/flutter (AF/AFl) recurrences in several multi-center trials. In addition to its rhythm control properties, dronedarone has rate control properties and slows the ventricular response during AF. Dronedarone is approved in Europe for rhythm and rate control indications. In patients with decompensated heart failure, dronedarone treatment increased mortality and cardiovascular hospitalizations. However, when dronedarone was used in elderly high risk AF/AFl patients excluding such high risk heart failure, cardiovascular hospitalizations were significantly reduced and the drug was approved in the USA for this indication in 2009 by the Food and Drug Administration. Updated guidelines suggest dronedarone as a front-line antiarrhythmic in many patients with AF/Fl but caution that the drug should not be used in patients with advanced heart failure. In addition, the recent results of the PALLAS trial suggest that dronedarone should not be used in the long-term treatment of patients with permanent AF.

**Keywords:** dronedarone, atrial fibrillation, amiodarone

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# Introduction

Dronedarone is an antiarrhythmic medication used for the treatment of atrial fibrillation (AF) and atrial flutter (AFL) and in the reduction of cardiovascular hospitalizations in high risk AF patients. This paper reviews the clinical pharmacology, electrophysiology, clinical trial data, efficacy and adverse effects of this new antiarrhythmic agent.

## Electrophysiological Properties

Dronedarone is a non-iodinated benzofuran derivative of amiodarone with similar multichannel blocking electrophysiologic properties[1–22] (Fig. 1). Like amiodarone, it has Class III effects, inhibiting the potassium currents $I_{Kr}$, $I_{Ks}$, $I_{K1}$, and $I_{KAch}$ and does not have reverse use-dependence.[12,13] Dronedarone is a 100 times more potent inhibitor than amiodarone in blocking the $I_{KAch}$ channel.[16] Similar to amiodarone, dronedarone demonstrates use-dependent block of the maximum upstroke velocity ($V_{max}$) of the papillary muscle,[12] suggesting block of the fast inward $I_{Na}$. In vitro studies showed that concentration of dronedarone to produce inhibition equivalent to amiodarone was approximately 10 fold lower.[21] Under whole-cell patch clamp on human atrial myocytes, amiodarone inhibited $I_{Na}$ by only 41% at 3 μM while dronedarone inhibited $I_{Na}$ by 97% at 3 μM.[21] Thus, in vitro studies demonstrate that the blocking effects of the two drugs on different channels are not equivalent. Dronedarone is a more potent inhibitor of slow L-type Ca channel (class IV activity) when compared to amiodarone, with the inhibitory concentration 50% of dronedarone being 50 times

less than amiodarone.[15] Dronedarone is an antagonist of $\alpha$- and $\beta$-adrenoceptors and thus exhibits class II activity,[20] but has less β1 adrenoreceptor antagonistic effect compared to amiodarone. In conscious dogs with healed myocardial infarction, dronedarone displayed antiadrenergic actions comparable to those of amiodarone and both drugs reduced exercise-induced tachycardia and decreased isoproterenol-induced tachycardia without impairing rest left ventricular function.[23]

Sustained administration of dronedarone increases the QTc interval and has been shown to exhibit less reverse use-dependency of repolarization than amiodarone.[12] Similar to amiodarone, dronedarone decreases the transmural dispersion of repolarization (TDR) by blocking both $I_{Kr}$ and $I_{Ks}$ and late sodium channels.[22] By blocking late $I_{Na}$, dronedarone has minimal effects on epicardial and endocardial action potentials but produces a marked effect on the action potential of M cells. The net effect is that dronedarone induces a small increase in action potential duration of endocardium and epicardium, with little effect in the M cells and homogenizes the transmural dispersion in refractoriness. The risk of proarrhythmia is further lowered by inhibiting slow L-type Ca channel, the minimal effect on reverse use-dependence and significantly reducing early after depolarization (EAD) and delayed after depolarization (DAD) induced by dofetilide and strophantidine in dog Purkinje fibers.[22] The above basic electrophysiology of dronedarone predicts a low risk of dronedarone-induced torsade de pointes.

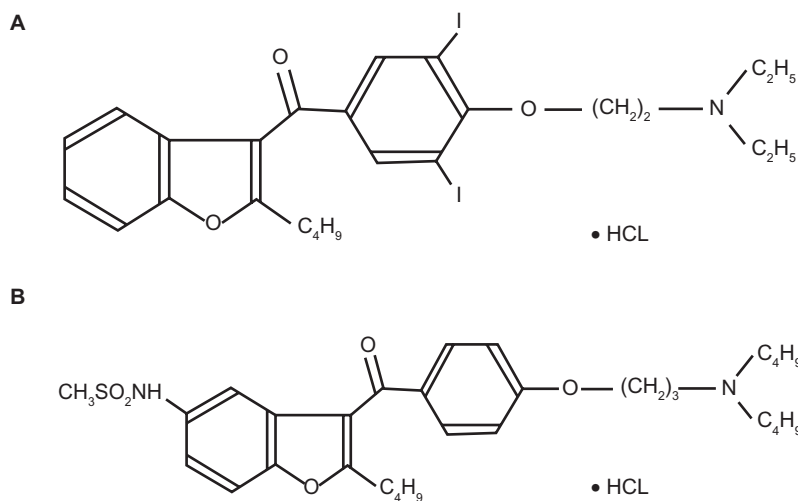The net electrocardiographic manifestations of dronedarone effect include sinus rate slowing,



**Figure 1.** Chemical structure of amiodarone and dronedarone (Reproduced with permission).[2]

PR prolongation and mild QTc prolongation with little effect on QRS duration.

Basic studies have demonstrated that drone-darone can suppress ischemia-induced ventricular arrhythmias.[24–26] In a rat model of ischemia, drone-darone significantly reduced the incidence of ventricular fibrillation from 80% to 30% ($P < 0.05$) at 3 mg/kg and eliminated ventricular fibrillation and mortality at 10 mg/kg.[24] On reperfusion, dronedarone reduced the incidence of mortality (from 90% to 20%, $P < 0.01$) at 1 mg/kg and eliminated ventricular fibrillation and mortality when administered at 3 and 10 mg/kg. In anesthetized pigs, dronedarone was more potent than amiodarone in reducing ischemia-induced ventricular arrhythmias.[26]

## Pharmacokinetics and metabolism of dronedarone

Dronedarone is N-[2-butyl-3[4-(3-dibutylamino-propoxy)benzoyl]-benzofurane-5-yl] methanesulfon-amide hydrochloride. Dronedarone differs structurally from amiodarone in that the iodine moiety has been removed and a methane-sulfonyl group has been added (Fig. 1). These modifications were made in an effort to reduce the thyroid and other end-organ adverse effects associated with amiodarone. The addition of the methane-sulfonyl group makes dronedarone less lipophilic, greatly shortening its half-life.[1,2]

After oral administration, approximately 70% to 94% of dronedarone is absorbed and absorption increases 2–3 fold when it is taken with food (especially high fat). Dronedarone's bioavailability is relatively low (about 15%) because of extensive hepatic first-pass metabolism by cytochrome P450 CYP3A4 and CYP2D6, thus requiring twice-daily dosing to achieve steady-state serum levels.[27] Only 6% of dronedarone is excreted via a renal route and it does cross the blood-brain barrier or the placenta and is excreted into breast milk. Dronedarone and its active N-debutyl metabolite are highly protein bound and the volume of distribution of dronedarone is 1200–1400 L. Steady state plasma concentrations of 84–167 ng/mL are reached in 7 days and the terminal elimination half-life of the drug varies from 13 to 31 hours.[5] Based on data from trials, the only recommended dose is 400 mg twice daily with meals and no dose adjustment has been proposed for age, gender, race, or renal function.

Dronedarone, similar to amiodarone, partial inhibits the tubular transport of creatinine, resulting in slightly increased (10%–20%) creatinine levels.[28] However, dronedarone has no meaningful effect on renal function as measured by the glomerular filtration rate.

## Drug-interactions

Drugs that interact with dronedarone and interaction mechanisms are summarized in Table 1. Dronedarone is highly metabolized by CYP3A4 and dronedarone is a moderate inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. Dronedarone has interactions with other drugs using the CYP450 systems.[5] Dronedarone should not be administered at the same time with potent CYP3A4 inhibitors including antifungals, macrolide antibiotics and protease inhibitors, since CYP3A4 inhibition may increase plasma levels of dronedarone and cause unwanted adverse effects. Dronedarone can be coadministered with moderate CYP3A4 inhibitors such as verapamil and diltiazem, but with some caution including using lower doses of these drugs.

Similar to amiodarone, dronedarone is a P-glycoprotein inhibitor and can increase the level of digoxin and dabigatran if co-administered together (Table 2). Since digoxin levels can double, digoxin doses should be cut in half if dronedarone is added to avoid digitalis toxicity.[29] Dabigatran levels can

**Table 1.** Cardiovascular drug interactions with dronedarone.*

| Drug | Mechanism | Effect | Dose adjustment |
|------|-----------|--------|-----------------|
| Digoxin | P-g P substrate | 2.5-fold increase digoxin level | Halve the digoxin dose |
| Verapamil, diltiazem | CYP3A inhibitors | 1.4 to 1.7 fold increase in dronedarone level | Lower dose of calcium channel blocker dose |
| β blockers | CYP2D6 substrate | 1.6 fold increase in metoprolol level | Lower β blocker dose |
| Simvastatin | CYP3A substrate | Up to 4-fold increase in simvastin level | Maximum simvastatin dose 10–40 mg |
| Dabigatran | P-g P Substrate | 1.1-1.9 increase in dabigatran level | Consider lower dose of dabigatran |

**Note:** *Modified from reference 7.
**Abbreviations:** P-g P, P-glycoprotein; CYP, cytochrome.

**Table 2.** Similarities and differences between amiodarone and dronedarone.*

| | Amiodarone | Dronedarone |
|---|---|---|
| Iodine moiety | Yes | No |
| Elimination half life | 53 days | 14–30 hours |
| Lipophilic properties | Strong | Moderate |
| Tissue accumulation | Yes | No |
| Blocks $I_{Kr}$; $I_{Ks}$; $B_1$; $I_{Ca}$; $I_{to}$; $I_{Na}$ | Yes | Yes |
| Dosing | Daily after loading | Twice daily with meals |
| Food effect | Yes | Yes |
| CYP4503A4 metabolism | Yes | Yes |
| Increases creatinine | Yes | Yes |
| Increase QT but low TDP | Yes | Yes |
| Efficacy in suppressing AF | 65% | 50% |
| Rate control in AF | Yes | Yes |
| Efficacy in suppressing ventricular tachyarrhythmias | Yes | Probably |
| Decreases CV hospitalization | No | Yes |
| Warfarin interaction | Yes | No |
| Dabigatran interaction | Yes | Yes |
| Digoxin interaction | Yes | Yes |
| Simvastatin interaction | Yes | Yes |
| Pulmonary/thyroid toxicity | Yes | No |
| Hepatic toxicity | Yes | Yes |
| Safety concerns in CHF | SCD-HeFT (NYHA III) | ANDROMEDA |

**Note:** *Modified from references 7, 45.
**Abbreviations:** TDP, torsade de pointes; AF, atrial fibrillation; CV, cardiovascular; CHF, congestive heart failure.

increase up to 1.9 times but currently no dose adjustment is recommended, although some clinicians have recommended taking the drugs 2 hours out of phase with each other in an attempt to avoid a peak to peak drug interaction.

Warfarin is a mixture of the S enantiomer, which is approximately 3 times more potent than the R enantiomer, and is metabolized primarily by CYP2C9. Inhibition of CYP2C9 by amiodarone and desethylamiodarone potentiates the anticoagulant effects of warfarin, increasing the risk of serious bleeding. Dronedarone does not significantly inhibit CYP2C9 and thus does not have clinically significant interaction with warfarin (Table 2). In healthy subjects, dronedarone at a dose of 600 mg twice daily increased S-warfarin exposure by 1.2-fold with no change in R-warfarin and with no clinically significant increase in INR.[30] In clinical trials in patients with AF/AFL, there was no observed excess risk of bleeding compared to placebo when dronedarone was co-administered with oral anticoagulants. DIONYSOS was the only trial that performed a head-to-head comparison between dronedarone and amiodarone.[31] In the dronedarone arm, the risk of hemorrhagic events was approximately 50% lower (HR = 0.504 [0.266–0.954]). There were 14 of 249 hemorrhagic events in the dronedarone group and 29 of 255 in the amiodarone group ($P = 0.03$). The incidence of lower hemoglobin level values was 4.7% in amiodarone arm as compared to 1.3% in the dronedarone arm. The amiodarone group also required more frequent downward adjustments in warfarin dose from day 5 to the end of study period. At day 10, doses of anticoagulants were decreased for approximately 48% of patients in the amiodarone group as compared to 20% in the dronedarone group. Patients with INR values greater than 4.5 were more common in the amiodarone group. At day 10, approximately 25% of patients in amiodarone group had INR values greater than 4.5 as compared to 9% in the dronedarone group. One intracranial hemorrhage was reported in the amiodarone group versus none in the dronedarone group. Since market release, anecdotal increases in INR have been reported in patients taking dronedarone, so close monitoring of INR levels is still recommended.

Dronedarone also interacts with commonly prescribed drugs such as metoprolol and simvastatin (Table 1). Dronedarone can increase serum simvastatin levels 2 to 4 fold and thus promote statin-induced myalgia. Recently, it has been recommended that simvastatin doses should be low (10 mg a day) in

patients taking simvastatin in combination with amiodarone. No specific recommendation was made for the use of simvastatin with dronedarone. We recommend using simvastatin doses no higher than 10–40 mg a day when used in conjunction with dronedarone. Since dronedarone interactions with atorvastatin and rosuvastatin are less marked and there is no significant interaction with pravastatin, these lipid lowering agents are safer to use in combination with dronedarone.

Metoprolol and dronedarone interact via-CYP2D6 inhibition that results in an increased bio-availability of metoprolol.[32]

## Clinical Trials

The initial dronedarone trials including DAFNE,[33] EURIDIS/ADONIS,[34] and ERATO[35] were designed to help establish efficacy, dosage and rate control (Table 3).

## DAFNE (dronedarone atrial fibrillation study after electrical cardioversion)[33]

In DAFNE, doses of 400 mg, 600 mg or 800 mg were given twice a day. This study included patients with long-standing persistent AF (82–122 days) who were randomized to the stated doses or placebo. Patients were electrically converted if they were still in AF 5–7 days after initiation of medication. The primary outcome was time to first documented AF recurrence, defined as an episode lasting for at least 10 min and documented by two distinct ECGs separated by the same time duration. Only with 800 mg/day of dronedarone was the time to first AF recurrence statistically ($P < 0.05$) prolonged from 5.3 days in the placebo group to 56.6 days in dronedarone group. The two higher dose dronedarone groups (1200 and 1600 mg/day) demonstrated no significant change in the time to first recurrence of AF, indicating a lack of dose effect. Another important finding of this trial was the poor medical conversion rate of dronedarone: which ranged from 5.8% with 800 mg/day dose to 14.8% with the maximum 1600 mg/d.

The main adverse effects were gastrointestinal in nature (nausea and diarrhea) and these side effects were dose-dependent. The lowest dose (400 mg twice daily with meals) was found to have the best efficacy, and was better tolerated with less gastrointestinal side effects. Based on this finding, future trials were all planned with 400 mg twice daily with meals. Very little dose ranging information is otherwise available

and lower doses of dronedarone have not been well-studied.

## EURIDIS (The European trial in atrial fibrillation or flutter patients receiving dronedarone for the maintenance of sinus rhythm) and ADONIS (the American-Australian-African trial with dronedarone in atrial fibrillation or flutter patients for the maintenance of sinus rhythm) trials[34]

Based on the results of DAFNE, dronedarone was 400 mg twice a day was used in EURIDIS (European trial) and ADONIS (American-Australian-African trial). These two identical trials involved patients with paroxysmal and persistent AF (underwent successful electrical cardioversion and remained in sinus rhythm for at least 1 hour). Previous treatment with amiodarone was permitted, and patients could be enrolled within 48 hours of amiodarone discontinuation. Important exclusion criteria were permanent AF, bradycardia less than 50 BPM, history of torsade de pointes, PR greater than 0.28s, second degree or higher AV block, CHF NYHA class III or IV, creatinine level of 1.7 mg per deciliter or greater. The total number of patients included in both trials was 1237, with 828 treated with dronedarone therapy due to a 2:1 dosing regimen with placebo. For the two trials combined, the median times to a documented recurrence of AF was 116 days in the dronedarone group and 53 days in the placebo group ($P < 0.05$). At 12 months, the maintenance of sinus rhythm with dronedarone was modest with rates of recurrence of 64.1% in the dronedarone group and 75.2% in the placebo group ($P < 0.001$). When compared to placebo, there was evidence of a rate controlling effect of dronedarone of 14 bpm in cases where AF recurred.

Hyperthyroidism occurred more frequently in the placebo group (14.1%) than the dronedarone group (8.4%) ($P < 0.002$). Mild QT and QTc prolongation (23 and 9 ms respectively) was noted but there were no reported episodes of torsade de pointes in the dronedarone treated patients. No end organ toxicity was reported including a similar incidence of elevated liver function tests in the dronedarone and placebo arms of the study.

ADONIS/EURIDIS demonstrated a significant increase in the median time to first recurrence of AF,

**Table 3.** Clinical trials investigating efficacy of dronedarone.

| Trial | Number of pts and follow up | Inclusion criteria | Main exclusion criteria | Results | Conclusion |
|---|---|---|---|---|---|
| DAFNE Placebo vs. dronedarone 40, 600, 800 mg BID | 270 pts 6 m f/u | Persistent AF (<12 m) average AF duration only 122 days | AFL, NYHA class III or IV, EF < 35% | First AF recurrence 800 mg –60 days vs. Placebo –5.3 days 1200,1600 mg/d-no difference from placebo | Lack of dose effect, modest efficacy, no TdP or organ toxicity over short f/u |
| EURIDIS/ADONIS Placebo vs. dronedarone 400 mg BID | 612 pts in EURIDIS 625 pts in ADONIS 12 m f/u | Paroxymal/ persistent AF | NYHA class III or IV, PR > 0.27 seconds, Heart rate < 50 bpm; Creatinine > 1.6 mg/dL | First AF recurrence D. 116 days P. 53 days. At 12 m recurrence D. 64.1% P. 75.2% $P < 0.001$ | Modest efficacy in healthy AF population Good safety over 12 m f/u |
| ERATO Placebo vs. dronedarone for rate control | 174 pts 6 m f/u | Permanent AF with resting HR > 80 bpm | NYHA class III or IV | Treatment effect on mean VR on day 14 –11.7 bpm; At maximal exercise –24.5 bpm | Heart rate reduction not associated with reduction in exercise tolerance |
| DIONYSOS | 504 pts 6 months f/u | Persistent AF | NYHA class III or IV, QTc > 500 ms, paroxymal AF/AFL, high degree AV block, thyroid disorder | AF recurrence or premature drug discontinuation for intolerance or lack of efficacy: D. 75.1% A. 58.8% AF recurrence at 12 months: D. 63.5% A. 42% | Dronedarone is significantly less effective than amiodarone but has fewer side effects and better tolerated |

**Abbreviations:** D, dronedarone; P, placebo; f/u, follow-up; AF, atrial fibrillation; TDP, torsade de pointes; bpm, beats per minute; pts, patients.

and a decrease in the ventricular response during AF recurrences. In addition, a retrospective analysis suggested that dronedarone decreased the composite endpoint of death and/or cardiovascular hospitalization.[34] ADONIS/SEURIDIS demonstrated that dronedarone statistically reduced the frequency of AF compared to placebo although the magnitude of effect was only about 25%. Although the magnitude of effect was significant, it did not appear to be as high as one would expect with amiodarone.

## Efficacy and safety of dronedarone for control of ventricular rate (ERATO) trial further established dronedarone's effectiveness in rate control of permanent atrial fibrillation[35]

The primary objective of ERATO was to assess the efficacy of dronedarone in the control of mean 24-hour ventricular rate in patients with permanent AF on day 14. Secondary objectives included assessment of the effects of dronedarone on heart rate during exercise, the impact of treatment on exercise tolerance, mean 24-hour ventricular rate at 4 months and the tolerability of dronedarone. Dronedarone reduced mean 24 hours ventricular rate by 11 BPM on day 14 compare to day 0 as opposed to increase by 0.7 BPM in placebo group. The prespecified subgroup analysis by concomitant rate-lowering medication revealed that HR was, in addition, lowered by dronedarone in patients receiving β-blocker, digoxin and calcium channel-blocker, with mean reductions in ventricular rate versus placebo of −14.9, −11.5, and −5.1 beat/min respectively. The least reduction of ventricular rate was in patients pretreated with calcium channel blockers.

At maximal exercise, there was a reduction in mean heart rate of 27.4 beat/min in the dronedarone group, compared with 2.9 beat/min in the placebo group ($P < 0.0001$) a treatment effect of 24.5 beat/min. The decrease in HR with dronedarone observed at day 14 was sustained during long-term treatment at 4 months.

## ANDROMEDA (antiarrhythmic trial with dronedarone in moderate to severe CHF evaluating morbidity decrease study)[36]

ANDROMEDA included systolic dysfunction patients (wall motion index 1.2 or less (approximating an ejection fraction of no more than 35%) with advanced CHF NYHA class III or IV or a heart failure related hospitalization) within 1 month before randomization. Enrollment and study treatment was prematurely discontinued for safety reasons on the recommendation of the data and safety monitoring board because of an increased number of deaths among patients who were assigned to dronedarone therapy (n = 25) as compared with those assigned to placebo (n = 12). Worsening heart failure was 5 times higher in dronedarone group than placebo, 10 pts (3.2%) and 2 pts (0.6%) respectively. The most powerful predictor of death was treatment with dronedarone. After an additional 6 months without study treatment, number of death was not statistically significant between the groups: 42 patients in the dronedarone group (13.5%) and 39 patients in the placebo group (12.3%) had died ($P = 0.60$).

Several explanations were proposed to explain study results. One explanation proposed by sponsor of the trial was withdrawal of ACE-I/ARBs. Detailed discussion of this hypothesis is beyond the scope of current review but increased mortality in ANDROMEDA trial cannot be attributed to inappropriate discontinuation of ACE-I or ARBs. In the placebo group, 50 patients were never on ACE-I or ARB and only 1 died (2%) versus in the dronedarone group 6 out of 16 patients naïve to ACE-I or ARB died (6%). An alternative explanation of the above results includes a chance effect in an under-powered study. The most likely explanation of ANDROMEDA is the negative inotropic effect of dronedarone lead to worsening of heart failure.[37] Dronedarone is strong $I_{Na}$ and $I_{Ca}$ channel inhibitor and the drug may have a stronger negative inotropic effect than amiodarone.

## 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)[38]

ATHENA was the largest antiarrhythmic drug trial (4628 patients) ever performed with an antiarrhythmic agent in AF/AFl. It was designed, in response to ANDROMEDA, to determine whether dronedarone would reduce the composite outcome of hospitalization due to cardiovascular events or death in patients

with AF. ATHENA was performed to focus on patients at risk of AF recurrence who may or may not have had heart failure, but would not have been randomized in the ANDROMEDA trial. Thus, key exclusion criteria for ATHENA was pulmonary edema within 12 hours, cardiogenic shock requiring intravenous pressors and/or mechanical ventilation or Class IV heart failure within 4 weeks. ATHENA was performed for several other regulatory reasons: (1) to verify the post-hoc result from ADONIS/EURIDIS that dronedarone prospectively could reduce the composite endpoint of cardiovascular hospitalizations/death; (2) to create a large database to show that dronedarone would be safe in a broad number of patients with structural heart disease; and, (3) to define a point estimate to show that this drug could be used safely in high risk AF/AFL patients excluding the ANDROMEDA population. Inclusion criteria included: The majority of the patients enrolled in ATHENA had normal or low normal EF and an EF of less than 45% was only present in 11.3% of the patients in dronedarone group and 12.5% in placebo group. A history of CHF, NYHA class II or III was present only in 20% in dronedarone group and 22% in placebo.

ATHENA demonstrated a statistical reduction in all-cause mortality or cardiovascular hospitalization in the dronedarone group. The hazard ratio was 0.76 (0.69–0.84; $P < 0.001$). Treatment with dronedarone results in one fewer death or cardiovascular hospitalization for every 12 patients treated for 21 months.

Even though dronedarone did not significantly reduce mortality [HR = 0.84 (CI 0.66–1.08)], cardiovascular death, sudden cardiac death, and death from stroke were all significantly reduced (Fig. 2). This finding was necessary for regulatory approval. The FDA mandates that drugs show a hazard ratio of less than 1.50 for any potential increase in mortality. There is minimal overlap of the mortality confidence intervals in the two trials with different patient populations. Thus, ATHENA properly excluded ANDROMEDA-like patients and dronedarone could safely be used in ATHENA-like patients. Sub-analyses of ATHENA showed favorable reductions of the primary endpoint in patients of NYHA III class, with ejection fractions of less than 35%, and also in those receiving diuretics, beta-blockers or ACE inhibitors. This dichotomy is highlighted in dronedarone's package insert that includes a box warning that contraindicates the use of dronedarone in ANDROMEDA-like patients.[39]

The primary outcome (the first hospitalization due to cardiovascular events or death from any cause) was strongly positive in favor of dronedarone ($P < 0.001$) but was driven heavily by the decrease in the number of first hospitalizations due to cardiovascular events, which was driven mainly by a reduction in the number of hospitalizations for AF (Fig. 3). There were also significantly fewer hospitalizations for an acute coronary syndrome in the dronedarone arm of the study. Death from any cause, one of the prespecified secondary endpoints, was less in dronedarone

| | Placebo n = 2327 | Dronedarone n = 2301 | HR | 95% CI | p value |
|---|---|---|---|---|---|
| **All death** | 139 | 116 | 0.84 | 0.66; 1.08 | 0.18 |
| **Non-CV death** | 49 | 53 | 1.10 | 0.74; 1.62 | 0.65 |
| **CV death** | 90 | 63 | 0.71 | 0.51; 0.98 | 0.03 |
| *Cardiac non-arrhythmic death* | 18 | 17 | 0.95 | 0.49; 1.85 | 0.89 |
| *Cardiac arrhythmic death* | 48 | 26 | 0.55 | 0.34; 0.88 | 0.01 |
| *Vascular non-cardiac* | 24 | 20 | 0.84 | 0.47; 1.52 | 0.57 |

**Figure 2.** Death, non-cardiovascular and cardiovascular death rates in ATHENA.[45]
**Abbreviation:** ACS, acute coronary syndrome.

| Reason for first CV hospitalization | Placebo n = 2327 | Dronedarone n = 2301 | HR | 95% CI | p value |
|---|---|---|---|---|---|
| **Any reason** | 859 | 675 | 0.74 | 0.67; 0.82 | <0.001 |
| *Atrial Fibrillation* | 510 | 335 | 0.63 | 0.55; 0.72 | <0.001 |
| *CHF* | 132 | 112 | 0.86 | 0.67; 1.10 | 0.22 |
| *ACS* | 89 | 62 | 0.70 | 0.51; 0.97 | 0.03 |
| *Syncope* | 32 | 27 | 0.85 | 0.51; 1.42 | 0.54 |
| *Ventricular arrhythmia or cardiac arrest* | 12 | 13 | 1.09 | 0.50; 2.39 | 0.83 |

**Figure 3.** Cardiovascular hospitalization rates in ATHENA.[45]
**Abbreviations:** ACS, acute coronary syndrome; CV, cardiovascular; CHF, congestive heart failure.

group than placebo (116 pts or 5% vs. 139% or 6%, $P = 0.18$). Cardiovascular death, other prespecified secondary endpoint, reached statistical significance in favor of dronedarone with absolute reduction only 1.2% (3.9% vs. 2.7% in placebo versus dronedarone group respectively). Further analysis of cardiovascular causes of death showed that dronedarone reduced sudden cardiac death, with a relative reduction 45% (2.1% in placebo group and 1.1% in dronedarone group),

suggesting a therapeutic effect of dronedarone in suppressing ventricular arrhythmias.

A post hoc analysis of the ATHENA data was done to investigate the effect of dronedarone on stroke risk in this population.[40] This analysis demonstrated that dronedarone reduced the risk of stroke from 1.8% per year to 1.2% per year (hazard ratio 0.66, 95% confidence interval 0.46 to 0.96, $P = 0.027$) (Fig. 4). The effect of dronedarone was similar, whether or not

| | Placebo | | Dronedarone | | HR | 95% CI | p |
|---|---|---|---|---|---|---|---|
| | # Events | Rate/Yr | # Events | Rate/Yr | | | |
| **Stroke** | 70 | 1.79% | 46 | 1.19% | 0.66 | 0.46−0.96 | 0.027 |
| **Stroke-related hospitalizations** | 55 | 1.4% | 38 | 1.0% | 0.69 | 0.46−1.05 | 0.082 |
| *Ischemic stroke* | 49 | 1.3% | 33 | 0.9% | 0.68 | 0.44−1.05 | 0.081 |
| *Hemorrhagic stroke* | 6 | 0.2% | 5 | 0.1% | 1.01 | 0.33−3.13 | 0.987 |
| **Stroke or TIA** | 80 | 2.05% | 53 | 1.37% | 0.67 | 0.47−0.94 | 0.020 |
| **Fatal stroke** | 21 | 0.54% | 14 | 0.36% | 0.67 | 0.34−1.32 | 0.247 |
| **Stroke, ACS or CV Death** | 216 | 5.52% | 147 | 3.80% | 0.68 | 0.55−0.84 | <0.001 |
| **Stroke, ACS or Death** | 262 | 6.70% | 196 | 5.06% | 0.75 | 0.62−0.90 | 0.002 |

**Figure 4.** Effect of dronedarone on stroke endpoints in ATHENA.[45]
**Abbreviations:** ACS, acute coronary syndrome; CV, cardiovascular; TIA, transient ischemic attack.

patients were receiving oral anticoagulant therapy, and there was a significantly greater effect of dronedarone in patients with higher $CHADS_2$ scores. In addition, there was a 31% reduction in stroke-related hospitalizations, a 32% reduction in ischemic stroke, and no difference in hemorrhagic stroke. Composites of stroke including stroke, acute coronary syndrome or cardiovascular death were also statistically reduced by dronedarone. Although the numbers were small, there were only 2 strokes in the permanent atrial fibrillation/atrial flutter population on dronedarone compared to 8 events in patients treated with placebo, who also had permanent atrial fibrillation. The decreased stroke risk in the dronedarone treated group of the ATHENA trial could be attributed to reduction of atrial fibrillation frequency. Dronedarone's modest reduction in blood pressure, and more substantial decrease in heart rate during atrial fibrillation are other potential mechanisms of decreased stroke risk.[41,42] The PALLAS trial, included composite stroke endpoints that were statistically worse on dronedarone therapy. The results of PALLAS raise the question of any stroke reduction benefit with dronedarone, although the populations studied were different.

ATHENA was a large safety trial designed to test whether dronedarone could be used in patients with atrial fibrillation and structural heart disease. The study enrolled patients with either persistent or paroxysmal AF and at least one cardiovascular risk factor. The same dose (400 mg twice a day) was used in this study as in ANDROMEDA. Patients with Class IV or recently decompensated heart failure were excluded. The results of ATHENA were significant reductions in the primary end points of all-cause mortality and cardiovascular hospitalization. The hazard ratio for the primary outcome in the dronedarone group was 0.76. The reduced rate of hospitalizations due to cardiovascular events was mainly attributed to fewer admissions for atrial fibrillation. In the dronedarone treated group the only significant adverse side effects were nausea, diarrhea, bradycardia, rash and QT prolongation. The rates of thyroid and pulmonary adverse events were no different from placebo.

## Post-ATHENA

In ATHENA, dronedarone reduced the primary endpoint of cardiovascular hospitalization [HR = 0.75 (CI 0.67–0.82)] although dronedarone had no effect on reducing hospitalizations for non-cardiovascular reasons [HR = 0.98 (CI 0.87–1.11)]. Although there was a decrease in cardiovascular hospitalization by suppression of AF and other supraventricular disorders [HR = 0.62 (CI 0.53–0.71)], the time to first cardiovascular hospitalization not due to AF/AFL was also increased [HR = 0.85 (CI 0.75–0.97)]. Thus, although AF admissions were reduced by 37% (HR 0.63; $P < 0.001$), a significant reduction in cardiovascular hospital admissions were secondary to non-arrhythmic causes; as an example, acute coronary syndrome admissions were decreased by 30% (HR 0.70; $P = 0.03$) (Fig. 3). Dronedarone also significantly decreased the risk of unplanned cardiovascular hospitalization and death from any cause by 24% (hazard ratio (HR) 0.76; $P < 0.001$) and decreased total unplanned cardiovascular hospitalization days by 28% ($P < 0.001$). This resulted in a 35% reduction ($P < 0.001$) in the total length of time spent in the hospital for cardiovascular reasons, including a statistical reduction of critical care, medium care, and ward days in hospital.[43] Another post-hoc analysis of ATHENA demonstrated a similar benefit in patients with lone AF.[44] Naccarelli et al reported that healthcare costs associated with CV hospitalizations and in patient deaths among ATHENA-like patients in the United States are high, with a mean of $10,908 per nonfatal admission.[45] Over a one year period, these 53.9% of these patients had a cardiovascular hospitalization. Thus a reduction in cardiovascular hospitalization in this population, by therapies such as dronedarone, would be expected to reduce health care costs.[46]

A post-hoc analysis of ATHENA demonstrated that dronedarone decreased unplanned cardiovascular hospitalization or death in permanent AF patients by 26% (HR = 0.74; $P = 0.096$).[47] The mechanism for this reduction might be secondary to the added rate control properties of dronedarone (mean ventricular response was 9 bpm lower, $P < 0.001$) or some other unknown mechanism. A large prospective randomized trial (PALLAS) is randomized permanent AF patients to dronedarone versus placebo. The co-primary endpoints of this study include the composite endpoint of stroke, systemic arterial embolism, myocardial infarction or cardiovascular death and a second composite endpoint of first unplanned cardiovascular hospitalization or death from any cause. This trial was

prematurely terminated due to adverse effects in the dronedarone arm of the study.

Although there has been concern in using dronedarone in patients with congestive heart failure, post-hoc analyses from the ATHENA trial[48] demonstrated a 22% reduction in cardiovascular hospitalization or death (HR = 0.78) in a small cohort of 209 patients with New York Heart II/III congestive heart failure and a left ventricular injection fraction of ≤40% at baseline. There was no difference between these 209 patients and the 4,335 patients without a history of heart failure or depressed ejection fraction who had a hazard ratio of 0.76 for unplanned cardiovascular hospitalization or death.

## DIONYSOS (efficacy and safety of dronedarone versus amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation)[31]

DIONYSOS recruited 504 patients with persistent AF over a median follow-up period of 7 months. The main exclusion criteria were previous chronic treatment with amiodarone, hypo- or hyperthyroidism, or other contraindications to amiodarone, (corrected QT (QTc)-interval ≥500 ms, paroxysmal AF/atrial flutter, New York Heart Association (NYHA) class III or IV congestive heart failure, severe bradycardia, or high-degree atrioventricular block.

The primary composite endpoint of the study was a measurement of efficacy, defined as recurrence of AF or premature study drug discontinuation for lack of efficacy. The main safety endpoint was the occurrence of adverse effects or premature study drug discontinuation following an adverse event. The incidence of the composite primary endpoint was 75.1% and 58.8% in the dronedarone and amiodarone groups, respectively, at 12 months treatment. The composite primary endpoint was mainly driven by the AF recurrence component which was more frequent in the dronedarone group compared with the amiodarone group (63.5% vs. 42.0%), while the premature drug discontinuation component was less frequent (10.4% vs. 13.3%, respectively). Fewer patients treated with dronedarone had spontaneous conversion (29 versus 83). In addition, the recurrence rate after conversion to sinus rhythm was 36.5% in the dronedarone group and 24.3% in the amiodarone group

and accounted for the majority of AF recurrences. The incidence of the meaningful side effects was 39.3% and 44.5% in the dronedarone and amiodarone groups, respectively. The dronedarone group had fewer thyroid, neurologic, skin, and ocular events but more gastrointestinal events, mainly diarrhea.

The DIONYSOS trial[31] showed that amiodarone was more effective in reducing atrial fibrillation recurrences post-cardioversion compared dronedarone. The dronedarone group tended to have a lower frequency of adverse events specifically less problems with thyroid disorders or bleeding from any warfarin interaction compared to amiodarone. In addition, a post hoc analysis of DIONYSOS demonstrated that dronedarone had a more favorable effect in reducing cardiovascular hospitalizations and death compared to the amiodarone limb of the study. This dichotomy in amiodarone having more effective antiarrhythmic properties for atrial fibrillation yet not having the same endpoint value compared to dronedarone probably relates to a combination of improved safety with dronedarone and some other properties, such as blood pressure lowering.[49] In the rhythm control arm of both AFFIRM and AF-CHF, with 62% and 82% amiodarone use respectively, there were statistically higher rates of cardiovascular hospitalizations[50–53] (Fig. 5). The high re-hospitalization rates were counter-intuitive given amiodarone's efficacy in suppressing AF recurrences. To highlight this dichotomy, in DIONYSOS, amiodarone was superior to dronedarone in preventing AF recurrences, but in AFFIRM and AF-CHF, amiodarone was ineffective in reducing mortality and actually increased cardiovascular hospitalizations. However, in DIONYSOS, dronedarone was statistically inferior to amiodarone in AF prevention, but had a favorable effect on reducing cardiovascular hospitalizations in ATHENA.

## Dronedarone: antiarrhythmic efficacy and differences from amiodarone

Dronedarone is not as effective an antiarrhythmic drug in suppressing AF as amiodarone.[31] Some have suggested that dronedarone is not an effective antiarrhythmic agent.[54] However, dronedarone showed statistically beneficial antiarrhythmic effects compared to placebo in ADONIS/EURIDIS.[34] In post-hoc analyses of ATHENA,[55] dronedarone reduced a time to first cardioversion by 31% ($P < 0.001$), the time to

| | **AFFIRM** | **AF-CHF** | **ATHENA** |
|---|---|---|---|
| Amiodarone use | 63% of patients | 82% of patients | None |
| Total mortality | ⬌ | ⬌ | ⬌ |
| CV mortality | N/A | ⬌ | ⬇ $P = 0.03$ |
| Hospitalization | ⬆ $P < 0.001$ | ⬆ $P = 0.001$ | ⬇ $P < 0.001$ |
| Stroke | ⬌ | ⬌ | ⬇ $P = 0.027$ |

**Figure 5.** Cardiovascular outcomes in ATHENA versus AFFIRM, AF-CHF.[45]

first AF/AFl occurrence by 25% ($P < 0.001$), reduced the number of patients in permanent AF from 12.8% in placebo to 7.7% in dronedarone ($P < 0.001$). Several studies have demonstrated that dronedarone is less effective than amiodarone in preventing AF but safer and as effective as other commercially available membrane active antiarrhythmic agents in maintaining sinus rhythm[56–58] (Fig. 6). In a meta-analysis, dronedarone was less effective than amiodarone for the maintenance of sinus rhythm, but was associated with fewer adverse side effects necessitating discontinuation of the drug.[56] Additionally, there was a trend toward greater all-cause mortality associated with amiodarone use. In dronedarone treated patients,

the incidence of end organ toxicity, or symptomatic bradycardia resulting in termination of the drug, was not statistically different from the placebo group. However, the incidence of pulmonary and liver toxicity in the amiodarone users requiring drug discontinuation was also no different from placebo. Basic studies demonstrate that dronedarone is less effective than amiodarone is suppressing AF[59] but the addition of ranolazine to dronedarone added significant efficacy to either drug alone.[60] Further studies of this combination may lead to a safe, effective combination antiarrhythmic agent.

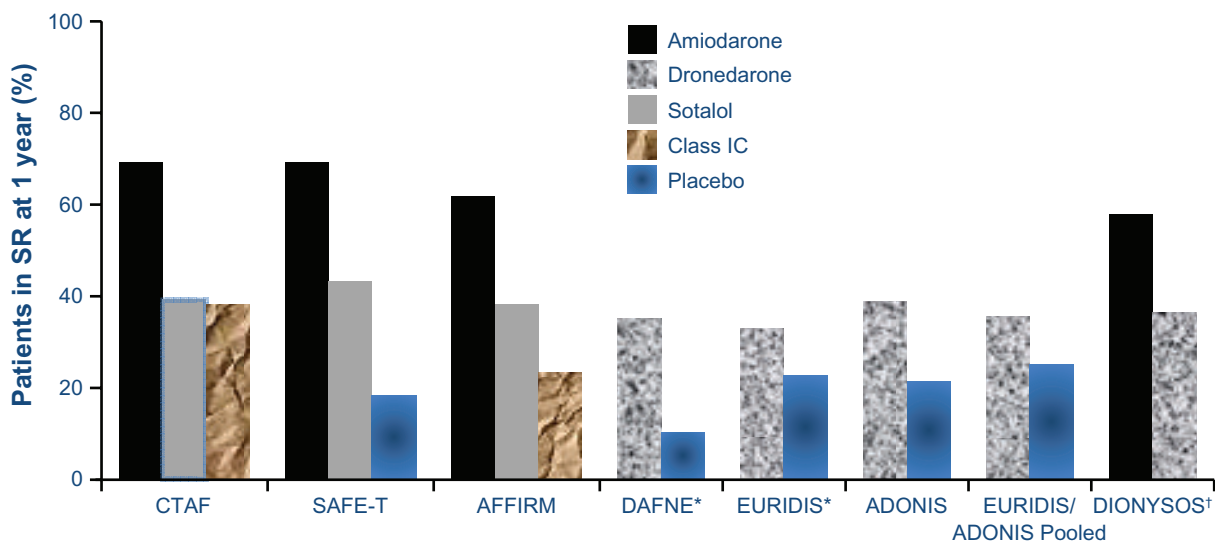Although dronedarone and amiodarone are both multichannel blockers with low-proarrhythmic profiles



**Figure 6.** Comparative efficacy of antiarrhythmic drugs including dronedarone in maintaining sinus rhythm in placebo-controlled or active-controlled trials. Modified from reference 10.
**Note:** *At 6 months; †Mean follow-up 7 months.
**Abbreviations:** CTAF, Canadian Trial of Atrial Fibrillation; SAFE-T, Sotalol Amiodarone Atrial Fibrillation Efficacy Trial; DAFNE, Dronedarone Atrial Fibrillation Study after Electrical Cardioversion; EURIDIS, European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm; ADONIS, American-Australian-African Trial with Dronedarone in Atrial Fibrillation or Flutter for the Maintenance of Sinus Rhythm; DIONYSOS, Randomized, Double-blind Trial to Evaluate the Efficacy and Safety of Dronedarone vs. Amiodarone for at least 6 months for the Maintenance of Sinus Rhythm in Patients with AF.

there are significant differences between the two drugs[5,6] (Table 2). Dronedarone has no iodine moiety and thus would not affect thyroid metabolism. Dronedarone has a shorter half life of 13–30 hours with no tissue accumulation. Dronedarone has coronary vasodilatation refractory to inhibition of the NO synthase pathway while amiodarone has coronary vasodilatation highly dependent on this pathway.[42] Dronedarone has a greater antihypertensive effect and no end organ toxicity or warfarin interaction. In addition it is important that dronedarone poses a different electrophysiologic profile to amiodarone. Although both drugs block inward sodium and calcium current and the outward potassium currents including the atrial-selective currents there is a different magnitude of the channel blocking effects of these two drugs.

The pleiotropic effects of dronedarone might partially be explained by its ability to decrease systolic and diastolic blood pressure by 2–3 mm of mercury Hg compared to placebo and amiodarone or through some other properties including heart rate slowing, coronary vasodilatation or properties that have yet to be determined. The mechanisms causing this blood pressure lowering are not completely understood. If blood pressure lowering explains some of the beneficial outcomes noted in ATHENA are speculative. Further studies into the mechanisms of action of dronedarone, in addition to its antiarrhythmic properties, may give us insight into the pleiotropic effects of this interesting multichannel blocking antiarrhythmic drug.

In ATHENA, cardiovascular mortality had a relative risk reduction of 30% with an absolute risk reduction of 1.13%. If we combine the annualized morbidity and mortality, the relative risk reduction using dronedarone in these patients is 25% with an absolute risk reduction of 7.5%. This compares favorably with other preventative trials in cardiology.[45] Future studies will clarify the mechanisms of this beneficial effect.

## Adverse effects

Although dronedarone has some potential for adverse effects, it appears to be safer than amiodarone. Since dronedarone was developed without any iodine moieties, it does not cause thyroid toxicity and thyroid monitoring is not required. There have been some post-marketing reports of interstitial lung disease and pneumonitis in dronedarone patients. Many of these patients had prior exposure to amiodarone. Pulmonary toxicity secondary to dronedarone appears to be rare and no certain causal relationship has been identified.

The most common adverse reactions from dronedarone appear to be gastrointestinal, including nausea (5.3%) and diarrhea (9.7%). Side effects are dose dependent. A combination of data from four clinical trials reported that amiodarone was associated with a greater all-cause mortality (OR: 1.61; CI: 0.97 to 2.68; $P \leq 0.066$) and greater overall adverse events requiring drug discontinuation versus dronedarone (OR: 1.81; CI: 1.33 to 2.46; $P < 0.001$).[41]

Dronedarone slows heart rate and prolongs AV nodal refractoriness and thus can increase the PR interval. Dronedarone cause very mild QTc prolongation and in clinical trial was not associated with increased risk of torsade de pointes. Although dronedarone prolongs the QT interval, the risk of torsades de pointes is low. There were no cases of torsades de pointes reported in the DIONYSOS trial and only one case in the ATHENA trial (in a patient with long QT syndrome). Similar to amiodarone, the low risk of torsades de pointes allows outpatient initiation of the drug. However, the risk of proarrhythmia could significantly increase in the setting of a $QT_c$ interval >500 ms, since such patients were excluded from the drug trials. Further studies, to define the safety of allowing such QT prolongation, are needed. Dronedarone should not be used in conjunction with other drugs that prolong the QT interval, and should be used cautiously with drugs known to interact with dronedarone. Periodic electrocardiograms are advised to monitor patients for a prolonged QT interval and bradycardia. Patients should be instructed to take dronedarone with food to increase absorption, and to avoid grapefruit juice.

Monitoring of liver function tests during controlled trials did not show any signal for hepatic toxicity. However, 2 cases of severe hepatocellular liver injury (out of over 300,000 drug exposures), including acute liver failure requiring transplant, has been reported in patients treated with MULTAQ in the postmarketing setting. Currently we are advising patients treated with dronedarone to report immediately symptoms suggesting hepatic injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper

quadrant pain, jaundice, dark urine, or itching). In the USA, we are obtaining baseline and periodic hepatic serum enzymes, especially during the first 6 months of treatment. It is not known whether routine periodic monitoring of serum enzymes will prevent the development of severe liver injury. If hepatic injury is suspected, we recommend prompt discontinuation of dronedarone and a search for a cause of hepatic injury. We are not restarting dronedarone in patients without another explanation for the observed liver injury. Patients with severe baseline hepatic impairment should not take dronedarone, since the drug is metabolized by the CYP450 system.

Although dronedarone was not found to be teratogenic in animal studies, dronedarone was not studied in pregnant women and is contraindicated for use during pregnancy. Due to the increased mortality in dronedarone treated patients in the ANDROMEDA trial, there is a box warning in the package insert against the use of the drug in patients with NYHA Class IV heart failure, or Class II-III heart failure with a recent decompensation requiring hospitalization or referral to a heart failure specialist.[39]

## Other potential indications for dronedarone

Amiodarone, in spite of being the most often prescribed medication for treatment of AF, is FDA approved only for therapy of ventricular arrhythmia. Dronedarone has been approved only for the treatment of AF and AFL. Dronedarone's electrophysiological effects on the ventricular myocardium are described above. However, there is limited data suggesting that dronedarone can be used for the treatment of ventricular arrhythmias.[61] Animal studies have demonstrated that dronedarone has antiarrhythmic properties in the ventricle.[24–26] In a post-myocardial infarction rat model, dronedarone was effective in suppressing ventricular arrhythmias.[62] In anesthetized rats, dronedarone at dose 10 mg/kg given intravenous completely suppressed incidence of VF and mortality during ischemic period and completely suppressed reperfusion induced arrhythmia. In a pig model of acute coronary occlusion dronedarone was more effect give than amiodarone, sotalol and lignocaine in preventing ventricular fibrillation.[26] Intravenous dronedarone was more effective than intravenous amiodarone in a rat model of ischemia and reperfusion-induced arrhythmias.[24] One small study in implantable cardioverter-defibrillator (ICD) patients showed no significant effect on defibrillation or pacing thresholds with doses up to 2000 mg/day. The ATHENA trial showed that dronedarone decrease cardiovascular mortality and a 45% reduction in sudden death. The effect of dronedarone on ventricular arrhythmias needs to be further studied in randomized trial. In the meantime, many physicians have treated patients with recurrent ICD shocks and concomitant ventricular arrhythmias with dronedarone. Sanofi is developing celivarone, a dronedarone analog, for the treatment of ventricular arrhythmias and no further large prospective trials are planned with dronedarone.

## Major Ongoing Trials
### ARTEMIS

Amiodarone is effective in suppressing AF in about 65% of patients but is often stopped secondary to inefficacy and adverse effects. Due to the risk of torsade de pointes associated with these drugs, and the long half-life of amiodarone, physicians have typically waited a month or more to start dofetilide or sotalol after stopping amiodarone. There is limited data from ATHENA and EURIDIS/ADONIS that patients can switch from amiodarone to dronedarone with minimal delay. In the ATHENA trial, patients had to stop amiodarone at least a month prior to enrollment in the trial. The earlier EURIDIS and ADONIS trials allowed patients to be enrolled immediately after discontinuation of amiodarone. Physicians are currently using their clinical judgment in deciding the optimal amiodarone washout period for each patient. n order to study the safety of this switch ARTEMIS is loading over 800 persistent AF patients with oral amiodarone for a month and following cardioversion are switching patients to dronedarone immediately, after one week and after one month. This study will help determine the safety of such antiarrhythmic drug switches.

### PALLAS

In a post-hoc analysis of ATHENA, dronedarone continued to demonstrate a benefit on decreasing cardiovascular hospitalizations in patients who developed permanent AF during the course of the study. Thus, decreased hospitalization may not be all secondary to preventing AF/AFl recurrences. Because of this

and in an attempt to better understand the benefit of dronedarone, PALLAS planned to enroll 10,800 patients with permanent AF/AFl and randomizing patients to dronedarone 400 mg twice daily with meals versus placebo. The co-primary composite endpoints of this study include: (1) first stroke, systemic arterial embolism, myocardial infarction or cardiovascular death; and, (2) first unplanned cardiovascular hospitalization or death from any cause. This study was prematurely halted, after 3,149 patients were enrolled, due to a two-fold increase in cardiovascular events (death, stroke, and hospitalization for heart failure) in the dronedarone arm of the study.[63]

## HESTIA
The Effects of Dronedarone on Atrial Fibrillation Burden in Subjects with Permanent Pacemakers (HESTIA) is a placebo controlled multicenter study assessing the effects of 400 mg twice daily of dronedarone on AF burden utilizing pacemaker electrogram data. The study duration is 12 weeks. The use of pacemaker electrograms will provide information on AF duration, frequency and relationship between AF burden and the patients' perceived AF burden. This study started in July 2010.

## Clinical Role of Dronedarone
In the USA, the Food and Drug Administration approved dronedarone on March 18, 2009, to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation or atrial flutter. In Europe the drug was approved for rhythm and rate control of AF. Some advantages of this new antiarrhythmic drug include ease of initiation, as well as less surveillance for end organ toxicity than amiodarone. There is a single recommended dose which can be started as an outpatient due to the low risk of proarrhythmia. While electrocardiograms should be periodically obtained, no chest x-rays or thyroid monitoring is required. Due to recent reports of possible rare hepatocellular injury, baseline liver function tests with periodic post-initiation checks are recommended. Since there is no significant interaction with warfarin, more frequent monitoring of INRs is not needed. Dronedarone can increase the blood levels of dabigatran and this interaction should be considered in patients taking concomitant therapy with these two drugs. Dronedarone is generally well tolerated.

Gastrointestinal side effects are the most common, but were responsible for discontinuation of the drug in only 3.2% of patients in clinical trials. In our experience, the rate of discontinuation from diarrhea and GI side effects is higher than this.

These factors, along with fewer hospitalizations and decreased stroke risk seen in the ATHENA trial, may result in decreased cost of treatment in dronedarone patients. On the other hand, DIONYSOS and other meta-analyses have shown dronedarone to be less effective than amiodarone in preventing recurrence of AF. Also, it was found to be unsafe for decompensated heart failure patients in the ANDROMEDA trial.

Although less efficacious than amiodarone in the prevention of recurrent AF, dronedarone appears to be a safer, well-tolerated drug in patients with preserved left ventricular function. Dronedarone can be considered as an alternative therapy to amiodarone, and used prior to amiodarone, especially in younger patients. Dronedarone is also an obvious choice for patients who have develop end-organ toxicity from amiodarone.

## Conclusion
Dronedarone is a first line therapy for patients with AF/AFl in patients.[64,65] The highest benefit/lowest risk patients appear to be those with structural heart disease, who have a preserved ejection fraction and no recent decompensated heart failure. Although it is less efficacious than amiodarone in maintaining sinus rhythm, its effectiveness is similar to the other antiarrhythmic drugs used to treat AF. Dronedarone has rate control properties that may help improve rate control in refractory patients and decrease their symptoms. However, the results of PALLAS suggest the drug should not be used in the long-term rate control of permanent AF patients. In the ATHENA-like population, the drug's cost can be counterbalanced by the lower cost of hospitalization. Based on ANDROMEDA, dronedarone should not be used in patients with CHF NYHA class III-IV and left ventricular systolic dysfunction. Dronedarone provides an additional option for patients with AF and can be considered earlier in the treatment algorithm than amiodarone in most patients except for those with advanced heart failure.

## Disclosures
Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal

and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

# References

1. Hodeige D, Heyndrickx JP, Chatelain P, Manning A. SR33589, a new amiodarone-like anti-arrhythmic agent: anti-adrenoceptor activity in anesthetized and conscious dogs. *Eur J Pharmacol*. 1995;279:25–32.
2. Hynes J, Wolbrette DL, Luck JC, Khan M, Samii S, Naccarelli GV. A review of the pharmacokinetics, electrophysiology and clinical efficacy of dronedarone. *Future Cardiology*. 2005;2(1):135–144.
3. Wegener FT, Ehrlich JR, Hohnloser SH. Dronedarone: An emerging agent with rhythm- and rate-controlling effects. *J Cardiovasc Electrophysiol*. 2006;17:S17–20.
4. Zareba KM. Dronedarone: a new antiarrhythmic agent. *Drugs Today*. 2006; 42:75–86.
5. Patel C, Yan GX, Kowey PR. New drugs and technology: Dronedarone. *Circulation*. 2009;120:636–44.
6. Zimetbaum PJ. Dronedarone for atrial fibrillation—an odyssey. *N Engl J Med*. 2009;360:1811–3.
7. Wolbrette D, Gonzalez M, Samii S, Banchs J, Penny-Peterson E, Naccarelli G. Dronedarone for the treatment of atrial fibrillation and flutter: approval and efficacy. *Vasc Health Risk Management*. 2010;6:517–23.
8. Patel DP, Bhuriya R, Patel DD, Singh PP, Arora RR. Dronedarone for atrial fibrillation: A new therapeutic agent. *Vasc Health Risk Management*. 2009; 5:635–42.
9. Dreskovich CD, O'Dell KM. Dronedarone for atrial fibrillation: An update of clinical evidence. *Formulary*. 2010;45:275–83.
10. Camm AJ, Savelieva I. Dronedarone: a new option in atrial fibrillation. *Future Prescriber*. 2009;10:24–32.
11. Manning A, Thisse V, Hodeige D, et al. SR33589, a new Amiodarone-like Antiarrhythmic Agent: Electrophysiological Effects in Anesthetized Dogs. *J Cardiovasc Pharmacol*. 2000;25:252–61.
12. Sun W, Sarma JS, Singh BN. Electrophysiological Effects of Dronedarone (SR33589), a Noniodinated Benzofuran Derivative, in the Rabbit Heart. Comparison with Amiodarone. *Circulation*. 1999;100:2276–81.
13. 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;39:677–84.
14. Varró A, Takács J, Németh M, et al. Electrophysiological effects of dronedarone (SR33589), a noniodinated amiodarone derivative in the canine heart: comparison with amiodarone. *Br J Pharmacol*. 2001;133:625–34.
15. Gautier P, Guillemare E, Marion A, et al. Electrophysiologic Characterization of Dronedarone in Guinea Pig Ventricular Cells. *J Cardiovasc Pharmacol*. 2003;41:191–202.
16. 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;36:802–5.
17. Altomare C, Barbuti A, Viscomi C, et al. Effects of dronedarone on Acetylcholine-activated current in rabbit SAN cells. *Br J Pharmacol*. 2000;130:1315–20.
18. Rocchetti M, Bertrand JP, Nisato D, et al. Cellular electrophysiological study of dronedarone, a new amiodarone-like agent, in Guinea pig sinoatrial node. *Nauyn Schmiedebergs Arch Pharmacol*. 1998;358(1 Suppl 2):R617.
19. Thomas D, Kathöfer 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;140:996–1002.
20. Hodeige D, Heyndrickx JP, Chatelain P, Manning A. SR33589, a new amiodarone-like antiarrhythmic agent: anti-adrenoceptor activity in anesthetized and conscious dogs. *Eur J Pharmacol*. 1995;279:25–32.
21. Lalevée N, Barrére-Lemaire S, Gautier P, et al. Effects of Amiodarone and Dronedarone on Voltage-Dependent Sodium Current in Human cardiomyocytes. *J Cardiovasc Electrophysiol*. 2003;14:885–90.
22. Verduyn SC, Vos MA, Leunissen HD, et al. Evaluation of the Acute Electrophysiological Effects of Intravenous Dronedarone, an Amiodarone-Like Agent, with Special Emphasis on Ventricular Repolarization and Acquired Torsade de Pointes Arrhythmias. *J Cardiovasc Pharmacol*. 1999; 33:212–22.
23. Djandjighian L, Planchenault J, Finance O, et al. Hemodynamic and anti-adrenergic effects of dronedarone and amiodarone in animals with a healed myocardial infarction. *J Cardiovasc Pharmacol*. 2000;36(3):376–83.
24. Manning AS, Bruynickx 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;26:453–61.
25. Rochetaing A, Barbé C, Kreher P. Beneficial Effects of Amiodarone and Dronedarone (SR33589b), when Applied During Low-Flow Ischemia, on Arrhythmia and Functional Parameters Assessed during Reperfusion in Isolated Rat Hearts. *J Cardiovasc Pharmacol*. 2001;38:500–11.
26. 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;26:570–6.
27. Dorian P. Clinical pharmacology of dronedarone: Implications for the therapy of atrial fibrillation. *J Cardiovasc Pharm Therap*. 2010;15(4S): 15S–8.
28. Tschuppert Y, Buclin T, Rothuizen LE, et al. Effect of dronedarone on renal function in healthy subjects. *Br J Clin Pharmacol*. 2007;64:785–91.
29. Vallakati A, Chandra PA, Pednekar M, Frankel R, Shani J. Dronedarone-induced digoxin toxicity: New drug, new interactions. *Am J Therap*. 2011; e published.
30. Shirolkar SC, Fiuzat M, Becker RC. Dronedarone and vitamin K antagonists: A review of drug-drug interactions. *Am Heart J*. 2010;160:577–82.
31. Le Heuzey JY, De Ferrari GM, Radzik D, Santini M, Zhu J, Davy JM. 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.
32. Damy T, Pousset F, Caplain H, Hulot JS, Lechat P. Pharmacokinetic and pharmacodynamic interactions between metoprolol and dronedarone in extensive and poor CYP2D6 metabolizers healthy subjects. *Fundam Clin Pharmacol*. 2004;18(1):113–23.
33. Touboul P, Brugada J, Capucci A, Crÿns HJ, Edvardsson N, Hohnloser SH. Dronedarone for prevention of atrial fibrillation: a dose-ranging study. *Eur Heart J*. 2003;24:1481–7.
34. Singh BN, Connolly SJ, Crijns HJ, et al. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med*. 2007;357: 987–99.
35. 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;156:527–9.
36. Køber L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med*. 2008;358: 2678–87.
37. Levine TB, Giles T, Radzik D, Ghali JK. Effect of dronedarone on exercise capacity and cardiac function in patients with severe left ventricular dysfunction and compensated heart failure. *Cardiovasc Drugs Ther*. 201;5–6: 449–58.
38. Hohnloser SH, Crijns HJGM, van Eickels M, et al; for the ATHENA Investigators. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med*. 2009;360:668–78.

39. Multaq package insert. 2011.

40. Connolly SJ, Crijns HJGM, Torp-Pedersen C, et al; for the ATHENA Investigators. Analysis of stroke in 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. *Circulation*. 2009;120:1174–80.

41. Christiansen CB, Torp-Pedersen C, Køber L. Impact of dronedarone in atrial fibrillation and flutter on stroke reduction. *Clin Intervent Age*. 2010;5:63–9.

42. Mason P, Jacob RF, Kubant R, Jacoby AM, Mizuno Y, Malinski T. Dronedarone enhances rat aortic and glomerular endothelial nitric oxide release in a dose-dependent manner. *J Am Collcardiol*. 2011;57(15):E1431 (abstract).

43. Torp-Pedersen C, Crijns HJGM, Gaudin C, Page R, Connolly SJ, Hohnloser SH; for the ATHENA Invesitgators. Impact of dronedarone on hospitalization burden in patients with atrial fibrillation: Results from the ATHENA trial. *Europace* 2011: e published.

44. Duray GZ, Torp-Pedersen C, Connolly SJ, Hohnloser SH. Effects of Dronedarone on Clinical Outcomes in Patients with Lone Atrial Fibrillation: Pooled Post Hoc Analysis from the ATHENA/EURIDIS/ADONIS Studies. *J Cardiovasc Electrophysiol* 2011; e published.

45. Naccarelli GV. Post-ATHENA and beyond. *J Intervention Card Electrophysiol*. 2011;31:55–60.

46. Naccarelli GV, Johnston S, Lin J, Patel P, Schulman K. Cost Burden of cardiovascular hospitalization and mortality in ATHENA-like patients with atrial fibrillation/atrial flutter in the United States. *Clin Cardiol*. 2010; 33(5):270–9.

47. Bauernfeind T, Erkapic D, Hohnloser SH. Innovative pharmacologic approaches to managing atrial fibrillation: The importance of reducing cardiovascular hospitalizations. *J Inn Card Rhythm Manage*. 2011;2: 173–7.

48. Hohnloser SH, Crijns HJGM, van Eickels M, et al; for the ATHENA Investigators. Dronedarone in patients with congestive heart failure: insights from ATHENA. *Eur Heart J*. 2010;31(14):1717–21.

49. Naccarelli GV, Wolbrette DL, Samii S, Banchs JE, Penny-Peterson E, Gonzalez M. Appropriate vs. Inappropriate Use of Dronedarone: Lessons Learned from Controlled Studies and Regulatory Review. *J Cardiovasc Pharmacol Ther*. 2010;15(4S):24S–30.

50. AFFIRM Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. *N Engl J Med*. 2002;347:1825–33.

51. Roy D, Talajic M, Nattel S, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008;358:2667–77.

52. Wyse DG, Slee A, Epstein AE, et al; and AFFIRM Investigators. Alternative endpoints for mortality in studies of patients with atrial fibrillation: the AFFIRM study experience. *Heart Rhythm*. 2004;1:531–7.

53. Slee A, Rathod S, Saksena S. Impact of a composite outcome analysis in evaluating atrial fibrillation treatment strategies: A current reassessment of the AFFIRM study. *Circulation*. 2009;120:S-692.

54. Singh D, Cingolani E, Daimond GA, Kaul S. Dronedarone for atrial fibrillation. Have we expanded the antiarrhythmic armamentarium? *J Am Coll Cardiol*. 2010;55:1569–76.

55. Page R, Connolly SJ, Crijns HJGM, et al. Rhythm- and rate-controlling effects of dronedarone in patients with atrial fibrillation (from the ATHENA trial). *Am J Cardiol*. 2011;107:1019–22.

56. Piccini JP, Hasselblad V, Peterson ED, Washam JB, Califf RM, Kong DF. Comparative efficacy of dronedarone and amiodarone for the maintenance of sinus rhythm in patients with atrial fibrillation. *J Am Coll Cardiol*. 2009;54:1089–95.

57. Freemantle N, Lafuente-Lafuente C, Mitchell S, Eckert L, Reynolds M. Mixed treatment comparison of dronedarone, amiodarone, sotalol, flecainide, and propafenone, for the management of atrial fibrillation. *Europace*. 2011;13:329–45.

58. Shukla A, Durand JB. Comparison of dronedarone and sotalol in preventing atrial fibrillation recurrence and maintaining sinus rhythm: A meta-analysis. *Heart Rhythm*. 2011;8(5):1547.

59. Burashnikov A, Belardinelli L, Antzelevitch C. Acute dronedarone is inferior to amiodarone in terminating and preventing atrial fibrillation in canine atria. *Heart Rhythm*. 2010;7(9):1273–9. *J Am Coll Cardiol*. 2010;56:1216–24.

60. Burashnikov A, Sicour S, Di Diego JM, Belardinelli L, Antzelevitch C. Synergistic effect of the combination of ranolazine and dronedarone to suppress atrial fibrillation. *J Am Coll Cardiol*. 2010;56:1216–24.

61. Shaaraoui M, Freudenberger R, Lavin V, Marchlinski FE. Suppression of ventricular tachycardia with dronedarone: A case report. *J Cardiovasc Electrophysiol*. 2011;22:201–2.

62. Aimond F, Beck L, Gauthier P, et al. Cellular and in vivo electrophysiologic effects of dronedarone in normal and postmyocardial infarction rats. *J Pharmacol Exp Ther*. 2000;292:415–24.

63. FDA drug safety communication 7/21/2011.

64. Wann LS, Curtis AB, January CT, et al. 2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (updating the 2006 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2011;123:104–23.

65. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369–429.