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The Role of Dronedarone in the Treatment of Atrial Fibrillation/Flutter in the Aftermath of PALLAS

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Abstract: Dronedarone is an amiodarone analog that differs structurally from amiodarone in that the iodine moiety was removed and a methane-sulfonyl group was added. These modifications reduce thyroid and other end-organ adverse effects and makes dronedarone less lipophilic, with a shorter 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. In patients with decompensated heart failure, dronedarone treatment increased mortality and cardiovascular hospitalizations. When dronedarone was used in elderly high risk AF/AFl patients, excluding those with advanced heart failure, cardiovascular hospitalizations were significantly reduced. The results of the PALLAS trial suggest that dronedarone should not be used in the long-term treatment of patients with permanent AF. Post-marketing data have demonstrated rare hepatic toxicity to be associated with dronedarone use. Updated practice and regulatory guidelines have positioned dronedarone as a front-line antiarrhythmic in many patients with AF/Fl. However, the drug should not be used in patients with advanced heart failure and in patients who develop permanent AF.

Keywords: Atrial fibrillation, dronedarone.

INTRODUCTION

Dronedarone is an antiarrhythmic medication used for the treatment of atrial fibrillation (AF) and atrial flutter (AFL) for the reduction of cardiovascular hospitalizations in high risk AF patients. This paper reviews clinical trial data and illustrated how the results of these trials and post-market release data have altered the recommendations for use of this agent.

CLINICAL TRIALS

The initial dronedarone trials including DAFNE [1], EURIDIS/ADONIS [2], and ERATO [3] were designed to establish efficacy, dosage and rate control (Table **1**).

DAFNE (Dronedarone Atrial Fibrillation Study After Electrical Cardioversion)

In DAFNE [1], doses of 400 mg, 600 mg or 800 mg were given twice a day. This study included patients with paroxysmal and persistent AF (82-122 days) who were randomized to one of the above dronedarone 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 electrocardiograms. The 800 mg/day dose statistically ($p<.05$) prolonged the time to first AF recurrence from 5.3 days in the placebo group to 56.6 days in the dronedarone group. The two higher dose dronedarone groups demonstrated no significant improvement in the time to first recurrence of AF and had a higher incidence of gastrointestinal adverse effects. The medical conversion rate of persistent AF to sinus rhythm with oral dronedarone ranged from 5.8% with 800 mg/day dose to 14.8% with the maximum 1600 mg/d.

Based on these findings, all subsequent trials used 400 mg. twice daily with meals. Very little dose ranging information is 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

EURIDIS (European trial) and ADONIS (American-Australian-African trial) [2] enrolled patients with paroxysmal and persistent AF who 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, torsade de pointes, PR greater than 0.28 s, second degree or higher AV block, CHF NYHA class III or IV, and a 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

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1875-6557/14 $58.00+.00

Table 1. 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 daily-60 days vs. Placebo -5.3 days. 1200,1600 mg/d-no difference from placebo.	Lack of dose effect, modest efficacy in preventing first recurrence in persistent AF, with 400 mg bid/meals.
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 preventing AF recurrence in patients with minimal SHD. Good safety over 12 mon 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	Rate control properties in addition to digoxin, beta-blockers and Ca-blockers.
DIONYSOS Dronedarone vs. Amiodarone	504 pts 6 month 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 significantly less effective than amiodarone but fewer side effects and better tolerated.
ATHENA Dronedarone vs. Placebo	4648 pts F/u: mean of 21 months	Elderly patients with Paroxysmal or persistent AF/AFl plus risk factors	Permanent AF; Decompensated heart failure	24% RR in cardiovascular hospitalizations (p<0.0001)	Dronedarone reduced hospitalizations in moderate risk, elderly patients with paroxysmal or persistent AF/AFl.
PALLAS Dronedarone vs. Placebo in Permanent AF	3236 out of planned 10,800 pts F/U: median 3.6 months	Permanent AF	Paroxysmal or Persistent AF	2.29 fold increase (CI: 1.34-3.94; p=0.002) in the primary composite CV endpoint (stroke, MI, systemic embolism, or CVdeath	Doubling of CV events with dronedarone in permanent AF.

Abbreviations: CV: cardiovascular; D: dronedarone; P: placebo; f/u: follow-up; AF/AFl: atrial fibrillation/flutter; MI: myocardial infarction; bpm: beats per minute; pts: patients. Modified from reference 9.

two trials combined, the median time to a documented recurrence of AF was 116 days in the dronedarone group and 53 days in the placebo group (p<.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 when AF recurred. No end organ toxicity was reported including a similar incidence of elevated liver function tests in the dronedarone and placebo

arms of the study. A retrospective post-hoc analysis suggested that dronedarone decreased the composite endpoint of death and/or cardiovascular hospitalization [2]. These findings formed the hypothesis of an outcome study, ATHENA, to be described later.

EFFICACY AND SAFETY OF DRONEDARONE FOR CONTROL OF VENTRICULAR RATE (ERATO) TRIAL FURTHER ESTABLISHED DRONEDARONE' S EFFECTIVENESS IN RATE CONTROL OF PERMANENT ATRIAL FIBRILLATION

The primary objective of ERATO [3] was to assess the efficacy of dronedarone in the control of mean 24-hour ventricular rate in patients with permanent AF. Secondary objectives included assessment of the effects of dronedarone on heart rate during exercise, the impact of treatment on exercise tolerance, and mean 24-hour ventricular rate at 4 months.

Dronedarone reduced mean 24 hour ventricular rate by 11 BPM on day 14 compare to day 0 as opposed to an increase by 0.7 BPM in placebo group. 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<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)

ANDROMEDA [4] 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 and a heart failure related hospitalization within 1 month of randomization. The trial 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. The most powerful predictor of death was treatment with dronedarone.

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)

ATHENA was the largest antiarrhythmic drug trial (4628 patients) ever performed with an antiarrhythmic agent in AF/AFl [5]. ATHENA was designed to determine if dronedarone would reduce the composite outcome of hospitalization due to cardiovascular events or death in selected patients with AF. ATHENA focused on high risk elderly patients with co-morbidities, at risk of AF recurrence who may or may not have had heart failure, but who would not have been randomized in the ANDROMEDA trial. The key exclusion criteria for ATHENA were pulmonary edema within 12 hours, cardiogenic shock requiring intravenous pressors, and/or mechanical ventilation or Class IV heart failure within 4 weeks. The majority of the patients enrolled in ATHENA had normal or low normal EF. 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 the dronedarone group and 22% on 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<.001). Treatment with dronedarone resulted 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.

ATHENA properly excluded ANDROMEDA-like patients. Nevertheless, 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, but does not contraindicate the use of the drug in patients with less severe heart failure [6].

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, in turn driven mainly by a reduction in the number of hospitalizations for AF. There were 30% fewer hospitalizations for acute coronary syndrome in the dronedarone arm of the study. Death from any cause was less in dronedarone group than placebo (5% vs. 6%, P=0.18). Cardiovascular death reached statistical significance in favor of dronedarone with an absolute risk reduction of 1.2% (3.9% vs. 2.7 in placebo versus dronedarone group respectively). Further analysis of cardiovascular causes of death showed a dronedarone reduced sudden cardiac death risk, 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. During a mean follow-up period of 21 months, the rates of thyroid and pulmonary and hepatic adverse events on dronedarone therapy were no different than placebo.

A post hoc analysis of ATHENA investigated the effect of dronedarone on stroke risk [7]. 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). The effect of dronedarone was similar, whether or not 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. However, the

number of events in this post-hoc analysis was small. There were only 2 strokes in patients developing permanent AF/Fl population on dronedarone compared to 8 events in patients treated with placebo.

DIONYSOS (Efficacy & Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation)

DIONYSOS [8] recruited 504 patients with persistent AF but excluded previous chronic treatment with amiodarone, hypo- or hyperthyroidism, corrected QT (QTc) interval ≥ 500 ms. 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 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 efficacy 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) in the dronedarone group. Fewer patients treated with dronedarone had spontaneous, medical conversion of their persistent AF (29 vs. 83). The recurrence rate after conversion to sinus rhythm was 36.5% in the dronedarone group and 24.3% in the amiodarone group. The incidence of 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.

DIONYSOS [8] showed that amiodarone was more effective in reducing atrial fibrillation recurrences post-cardioversion compared to dronedarone. The dronedarone group tended to have a lower frequency of adverse events, specifically less problem 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 paradox of inferior efficacy but fewer hospitalizations/deaths may relate to a combination of improved safety with dronedarone and some other properties, such as blood pressure lowering. It should be noted that in the rhythm control arm of both AFFIRM and AF-CHF populated mainly by amiodarone treatment, there were statistically higher rates of cardiovascular hospitalizations than in the rate control arm or control group [9, 10].

HESTIA (The Effects of Dronedarone on Atrial Fibrillation Burden in Subjects with Permanent Pacemakers)

HESTIA [11] was 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 was 12 weeks. The use of pacemaker electrograms provides information on AF duration, frequency and relationship between AF burden and the patients' perceived AF burden. Preliminary data were recently presented at the American Heart Association Scientific Sessions, and showed that dronedarone reduces AF burden by 59%. HESTIA confirms previous findings that dronedarone is an effective atrial antiarrhythmic agent.

PALLAS (Permanent Atrial Fibrillation Outcome Study Using Dronedarone on Top of Standard Therapy)

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). The mechanism for this reduction might have been secondary to the added rate control properties of dronedarone or some other protective mechanism. PALLAS [12] planned to enroll 10,800 patients with permanent AF/AFl, randomizing patients to dronedarone 400 mg. twice daily with meals versus placebo. The co-primary composite endpoint of this study included: 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 2.29 fold increase (CI: 1.34-3.94; p=0.002) in the primary composite endpoint cardiovascular of the study (stroke, myocardial infarction, systemic embolism, or cardiovascular death) in the dronedarone arm of the study. In addition, dronedarone increased the second primary composite endpoint (HR 1.95(CI:1.45-2.62; p<0.001). These results occurred even though dronedarone reduced heart rate by 8 bpm and systolic blood pressure by 3.5 mm Hg at one month after initiation of therapy.

The reasons for these adverse results in PALLAS compared to the beneficial results with dronedarone in ATHENA are not known. In PALLAS about one-third of patients were receiving concomitant digoxin and their digoxin levels increased by 33% due to the dronedarone-digoxin interaction. If this interaction caused some adverse events is speculative. In addition to the permanent AF issue, PALLAS studied a patient population with more advanced cardiovascular disease, with >10% more coronary artery disease, 20% more patients with a history of stroke or TIA, and 16% more patients with LVEFs < 40%. These results highlight how little we know about the risk/benefit antiarrhythmic drug therapy in permanent AF. Based on the results of PALLAS, patients who develop permanent AF/AFl should have their dronedarone discontinued and package insert warning were added to emphasize this point.

HARMONY (A Study to Evaluate the Effect of Ranolazine and Dronedarone When Given Alone and in Combination in Patients With Paroxysmal Atrial Fibrillation)

In addition to DIONYSOS, several pre-clinical studies demonstrated that dronedarone is less effective than amiodarone is suppressing AF [13]. In these models, the addition of ranolazine to dronedarone added significant efficacy to either drug alone [14]. Based on these observations, HARMONY [15] will determine if the addition of ranolazine to dronedarone will add efficacy for the suppression of AF compared to either agent alone. About 150 patients will be

enrolled at 45 sites in North America and Europe, with the study estimated to complete in late 2013. HARMONY is designed to evaluate the effect of ranolazine and low dose dronedarone on AF burden when given alone and in combination in patients with previously implanted pacemakers and paroxysmal atrial fibrillation (PAF) over 12 weeks of treatment.

Post-Marketing Monitoring

Although dronedarone has some potential for adverse effects, it appears to be safer than amiodarone. 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, but in both the USA and Europe it has been recommended that dronedarone should not be given to patients who have had previous pulmonary toxicity due to amiodarone.

The most common adverse reactions from dronedarone appear to be gastrointestinal, including nausea (5.3%) and diarrhea (9.7%). Side effects are dose dependent and gastrointestinal intolerance remains one of the most frequent reasons dronedarone is discontinued.

Dronedarone slows heart rate and prolongs AV nodal refractoriness and thus can increase the PR interval or the heart rate in AF. Dronedarone causes QTc prolongation but in clinical trials torsade de pointes was exceedingly rare. The low risk of torsade de pointes and other toxicities permits outpatient initiation of the drug. Nevertheless, dronedarone should not be used in conjunction with other drugs that prolong the QT interval, and should be used cautiously with drugs known to increase dronedarone exposure.

Monitoring of liver function tests during controlled trials did not reveal a signal of hepatic toxicity. However, 2 cases of severe hepatocellular liver injury (in over 850,000 drug exposures), leading to acute liver failure requiring transplant, have been reported in patients treated with dronedarone in the post-marketing setting [16]. The FDA package insert [17] recommends advising patients treated with dronedarone to report symptoms suggesting hepatic injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain, jaundice, dark urine, or itching). In addition, baseline and periodic hepatic serum enzymes, especially during the first 6 months of treatment, is recommended. In Europe [18] more frequent liver function monitoring is advised. It is not known whether routine periodic monitoring of serum enzymes will prevent the development of severe liver injury. Patients with severe baseline hepatic impairment should not take dronedarone.

Due to the increased mortality in dronedarone treated patients in the ANDROMEDA trial, there is a black box warning in the package insert regarding 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. Due to multiple reports of heart failure worsening, published guidelines [19, 20] do not recommend using dronedarone in patients with a history of significant heart failure and/or systolic dysfunction.

CLINICAL ROLE OF DRONEDARONE POST-PALLAS

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 initially was approved for rhythm and rate control of AF. These recommendations have been altered post-PALLAS. In the US, dronedarone is currently approved to reduce the risk of hospitalization in patients in sinus rhythm with a history of paroxysmal or persistent AF. In Europe, dronedarone is indicated for the maintenance of sinus rhythm after successful cardioversion in clinically stable patients with paroxysmal or persistent AF. On both sides of the Atlantic Ocean, major contraindications include patients with symptomatic heart failure with recent decompensation or NYHA IV heart failure or in patients who have permanent AF.

Some advantages of this new antiarrhythmic drug include ease of outpatient initiation, a single dose, and less surveillance for end organ toxicity than amiodarone. 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. Although there is no consistent interaction of warfarin and dronedarone, there have been isolated reports of elevated INRs in patient taking warfarin after dronedarone was added. The mechanism of this interaction is not clear. An indirect interaction of altered gastrointestinal transit and/or diarrhea on dronedarone that alters vitamin K availability has been proposed. Dronedarone can increase the blood levels of dabigatran, rivaroxaban and apixaban by inhibiting the P glycoprotein transport pump and hepatic metabolism. In Europe, dronedarone's package insert suggests avoiding using of dabigatran and dronedarone in combination, while in the US, the package insert suggests using the lowest dose of dabigatran 75 mg twice daily if both drugs are used in a patient with altered renal function.

Although less efficacious than amiodarone in the prevention of recurrent AF, dronedarone appears to be a safer and 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.

CONFLICT OF INTEREST

Both authors (Naccarelli and Kowey) have been consultants to Sanofi.

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