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-sulfonil 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/AFl. 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
Table 1. Clinical trials investigating efficacy of dronedarone.

| Trial        | Number of pts and follow up | Inclusion criteria | Main exclusion criteria | Results                                      | Conclusion                                     |
|--------------|-----------------------------|-------------------|-------------------------|----------------------------------------------|-----------------------------------------------|
| DAFNE        | 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/meal. |
| EURIDIS/ ADONIS | 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 fu. |
| ERATO        | 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     | 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       | 4648 pts F/u: mean of 21 months | Elderly patients with Paroxysmal or persistent AF/AFI 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/AFI. |
| PALLAS       | 3236 out of planned 10,800 pts F/U: median 3.6 months | Permanent AF | Paroxymal 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.
within 12 hours, cardiogenic shock requiring intravenous treatment was exclusion criterion for ATHENA were pulmonary edema. Patients who have been randomized in the ANDROMEDA trial. The key exclusion criteria for ATHENA were pulmonary edema, 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<0.001). 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 anti-coagulant therapy, and there was a significantly greater effect of dronedarone in patients with higher CHADS2 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 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 events 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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REFERENCES

[1] Touboul P, Brugada J, Capucci A, Crijns HJ, Edvardsson N, Hohnloser SH. Dronedarone for prevention of atrial fibrillation: a dose-ranging study. Eur Heart J 2003; 24: 1481-7.

[2] 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.
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.

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.

Hohnloser SH, Crijns HJGM, van Eickels M, et al. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009; 360: 668-78.

Multaq package insert, www.multaq.com

Connolly SJ, Crijns HJGM, Torp-Pedersen C, et al. 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.

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.

Naccarelli GV, Wolbert DL, Levin V, et al. Safety and efficacy of dronedarone in the treatment of atrial fibrillation/flutter. Clin Med Insights Cardiol 2011; 5: 103-19.

Saksena S, Slee A, Waldo A, et al. Cardiovascular outcomes in the AFFIRM trial (Atrial Fibrillation Follow-Up Investigation of Rhythm Management). An assessment of individual antiarrhythmic drug therapies compared with rate control with propensity score-matched analysis. J Am Coll Cardiol 2011; 58: 1975-85.

Ezekowitz M, DiMarco J, Kaszala K, Ellenbogen K, Boddy A, Koren A. The Effects of Dronedarone on Atrial Fibrillation Burden in Subjects with Permanent Pacemakers HESTIA. Circulation 2012; 126: A15020.

Connolly SJ, Camm AJ, Halperin JL, et al. for the PALLAS Investigators. Dronedarone in high risk permanent atrial fibrillation. N Engl J Med 2011; 365: 2268-76.

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.

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.

clinical trials.gov/show/NCT01522651

Joghetaei N, Weirich G, Huber W, Buchler P, Estner H. Acute liver failure with dronedarone. Cire Arhythm Electrophysiol 2011; 4: 592-3.

FDA drug safety communication 7/21/2011. www.fda.gov/Drugs/DrugSafety/ucm264

European Medicines Agency. European Medicines Agency recommends restricting use of Multaq [press release]. September 22, 2011. www.ema.europa.eu/.../wc5000112800.pdf

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.

Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC guidelines for the management of atrial fibrillation. Eur Heart J 2012; 33(21): 2719-47.