



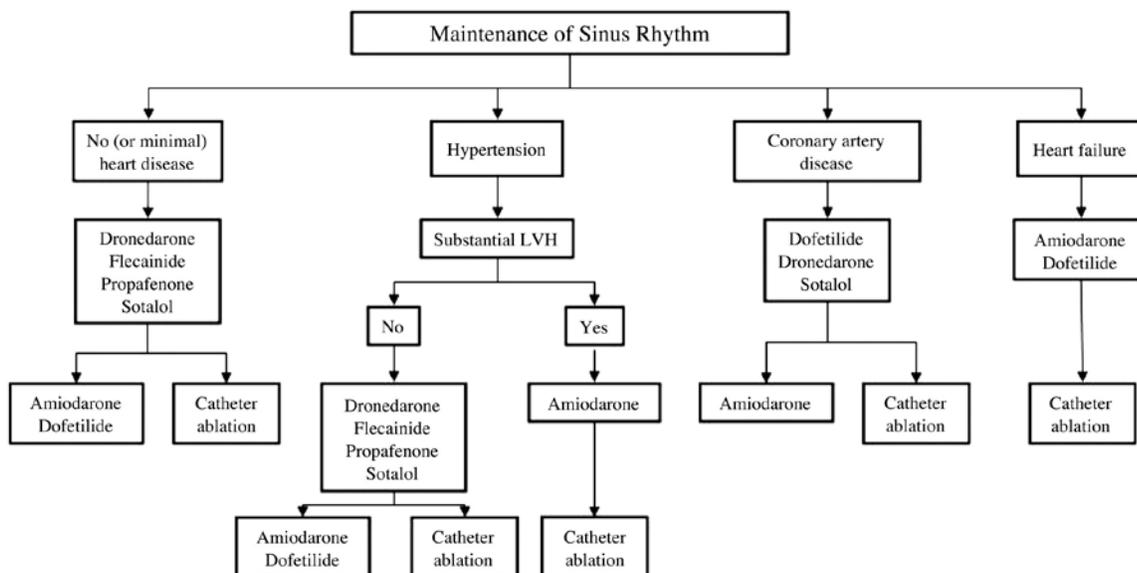
**Antiarrhythmic Agents:
Dronedaron (Multaq®) and Amiodarone
March 2011**



INTRODUCTION:

Atrial fibrillation (AF) is the most common form of cardiac arrhythmia, affecting more than 2 million people in the United States alone.¹ According to a study published in the Journal of the National Medical Association, the prevalence of AF among Native American males was 5.4%, nearly identical to the national average of 5.3%.² Major risk factors for AF include other heart conditions such as coronary artery disease, heart failure, structural and congenital heart defects and pericarditis. Other conditions that can increase the risk of AF include hyperthyroidism, obesity, diabetes and hypertension. The major complications of AF are stroke and heart failure. The goals of treatment for AF include control of rate and rhythm and prevention of stroke.¹ To reduce the risk of stroke, anticoagulation therapy is often used; to determine the patients risk and therefore need for this treatment the CHADS₂ (Congestive Heart Failure +1, Hypertension +1, Age over 75 +1, Diabetes +1, history of stroke +2) score is used. If the CHADS₂ score is ≥ 2 , anticoagulation therapy is usually initiated.³ Rate and rhythm control can be successfully attained through procedures, including cardioversion or catheter ablation, and through the use of various antiarrhythmic medications.¹ The following figure shows the treatment algorithm for rhythm control from the 2011 ACCF/AHA/HRS Focused Update on the Management of Patients with Atrial Fibrillation.⁴

Figure 1. Maintenance of Sinus Rhythm in Atrial Fibrillation⁴



PHARMACOLOGY/PHARMACOKINETICS:⁵⁻⁷

Mechanism of Action:

Dronedaron is a derivative of amiodarone that has had the iodine groups removed and a methane sulfonyl group added in order to reduce tissue accumulation and minimize adverse effects.

Dronedaron is a Class III antiarrhythmic agent with properties of all four Vaughan-Williams classes that inhibits sodium and potassium channels resulting in a prolongation of the action potential and refractory period in myocardial tissue. Inhibition of calcium and beta₁-receptor blockade results in a decrease in AV conduction and sinus node function.

Amiodarone is a Class III antiarrhythmic agent that prolongs the myocardial cell action potential duration and refractory period, decreases AV conduction and sinus node function and inhibits alpha- and beta-adrenergic stimulation. Amiodarone has effects on sodium, potassium and calcium channels.

Table 1. Pharmacokinetic Properties of Class III Antiarrhythmics⁵⁻⁶

Drug	Absorption	Distribution	Metabolism	Excretion
Dronedarone	Bioavailability: Fasting – 4% Fed state (high fat meal) – 15% Time to peak plasma concentrations (fed state) - 3-6 hours Steady state - 4-8 days	Plasma protein binding (mainly albumin) - >98% V_d - ~20L/kg	Extensive hepatic metabolism mainly through CYP3A4	Feces – 84% Urine – 6% Elimination half-life – 13-19 hours
Amiodarone	Slow and variable – rate and extent increased with food Bioavailability – 35-65% Time to peak plasma concentrations – 3-7 hours Onset of action – may occur in 2-3 days but is usually 1-3 weeks with loading dose	Plasma protein binding – 96% V_d - ~60L/kg – large and variable due to extensive accumulation in adipose tissue, liver, lungs and spleen	Hepatic metabolism through CYP3A4 and CYP2C8	Primarily through hepatic metabolism and biliary excretion Negligible excretion in urine Mean elimination half-life – 58 days (range 15-142 days)

FDA APPROVED INDICATIONS:⁵⁻⁶

Dronedarone is indicated to reduce the risk of hospitalization from cardiovascular causes in patients with paroxysmal or persistent atrial fibrillation (AF) or atrial flutter (AFL), with a recent episode of AF/AFL and associated cardiovascular risk factors, who are in sinus rhythm or will be cardioverted. Associated cardiovascular risk factors include age > 70 years, hypertension, diabetes, prior cerebrovascular accident, left atrial diameter greater than or equal to 50 millimeters, or left ventricular ejection fraction < 40%.

Amiodarone is indicated for the treatment of documented, life-threatening recurrent ventricular fibrillation and recurrent hemodynamically unstable ventricular tachycardia.

CURRENT NATIONAL CORE FORMULARY ALTERNATIVES:⁸

Currently no Class III Antiarrhythmic agents are available on the IHS National Core Formulary (NCF).

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Other antiarrhythmics available on the IHS NCF include class II beta-blocking agents (ex. carvedilol, atenolol, and metoprolol), class IV calcium channel blocking agents (ex. verapamil and diltiazem), and the class V antiarrhythmic digoxin.

DOSAGE AND ADMINISTRATION:⁵⁻⁷

Table 2. Dosing and Administration of Class III Antiarrhythmics⁵⁻⁶

Drug	Loading Dose	Adjustment Dose	Maintenance Dose	Special Populations	Hepatic Impairment	Renal Impairment
Dronedarone	N/A	N/A	1 tablet (400mg) BID taken with morning and evening meals. Discontinue treatment with Class I or III antiarrhythmics or strong inhibitors of CYP3A4 before starting dronedarone.	Geriatric Patients – follow adult dosing guidelines. Pediatric Patients – safety and efficacy not established in patients less than 18 years. Pregnancy – Category X. Contraindicated in nursing women.	Contraindicated in patients with severe hepatic impairment. No adjustment recommended for patients with moderate hepatic impairment.	No adjustment needed.
Amiodarone	800mg to 1600mg daily for 1 to 3 weeks until initial therapeutic response. Administer in divided doses with meals if total daily dose is > 1000mg or GI intolerance occurs. Gradually discontinue prior antiarrhythmic drugs when starting amiodarone.	600mg to 800mg daily for ~ 1 month. Begin this dose once adequate arrhythmia control is achieved or side effects become prominent.	400mg daily. Some patients may require up to 600mg daily or lower doses. Dose should be based on antiarrhythmic effects assessed by symptoms, Holter monitoring, or patient tolerance. Administer once daily unless severe GI intolerance occurs, then use BID.	Geriatric Patients – use caution in dose selection and start at low end of dosing range. Pediatric Patients – safety and efficacy not established in this population. Pregnancy – Category D. Nursing women advised to discontinue breastfeeding.	No specific guidelines available. Recommended to decrease dose with substantial hepatic impairment.	No adjustment needed. Not removed by dialysis.

EFFICACY:

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Clinical Trials:

ATHENA

Connolly et al included 4628 patients in a placebo controlled, double blind trial if they had either paroxysmal or persistent AF or AFL and at least 1 additional risk factor for CV events including: age over 75, age over 70 with at least 1 of the following: hypertension, diabetes mellitus, prior stroke or transient ischemic attack, left atrial enlargement (50 mm Hg), or depressed left ventricular ejection fraction (0.40).⁹ The patients were randomized to receive either dronedarone 400mg twice daily or placebo and were treated for a minimum of one year (mean follow-up of 21 months). The primary endpoint of the study was cardiovascular hospitalization or death due to any cause; secondary endpoints were death, cardiovascular death and cardiovascular hospitalization. A statistically significant reduction was found in the dronedarone group for total strokes; composite of strokes or transient ischemic attack (TIA); strokes, composite of acute coronary syndrome (ACS) or cardiovascular death; and the composite of stroke, ACS or death. There was no significant difference in the secondary endpoint of all-cause mortality. The effect of dronedarone was similar whether or not patients were receiving oral anticoagulation, and there was a significantly greater effect of dronedarone in patients with a CHADS₂ score of 2 or greater.

ANDROMEDA

Kober et al conducted a double blind trial that randomized 627 patients with NYHA Class III or IV heart failure (HF) to either dronedarone 400mg twice daily or placebo to determine the efficacy of dronedarone in reducing hospitalizations due to CHF in patients with symptomatic HF with a primary composite endpoint of death from any cause or hospitalization from HF.¹⁰ The study was designed to be conducted for two years, but after just two months it was terminated due to a significant increase in deaths that was seen in the dronedarone group. 8.1% of patients in the dronedarone group died as compared to 3.8% in the placebo group (p=0.03).

EURIDIS and ADONIS

Singh et al conducted a double blind, randomized trial that included 828 patients randomized to receive either dronedarone 400mg twice daily or placebo with a primary end point of time to recurrence of AF. Secondary end points included symptoms related to AF and the mean ventricular rate during the recurrence of AF.¹¹ Recurrence of AF occurred after 116 days in the dronedarone group (64.1% recurred after 12 months) and 53 days in the placebo group (75.2% recurred after 12 months, p=0.02). In the dronedarone group, heart rate was reduced by 6.8%, the QT interval was prolonged by 23.4 msec, and the QTc interval was prolonged by 9.0 msec (p<0.001 for all comparisons with the placebo group). The average heart rate during the first recurrence of AF was 102.3 +/- 24.7 bpm for the dronedarone group and 117.5 +/-29.1 bpm for the placebo group (p<0.001).

Meta-Analysis

Piccini et al. conducted a meta-analysis in 2009 that focused on 6 clinical trials.¹² The analysis found that amiodarone significantly reduced recurrent AF when compared to dronedarone (OR=0.16, CI=0.06-0.42) and calculated that there would be 360 fewer events per 1,000 patients treated with amiodarone. It was also found that amiodarone would prevent AF with greater efficacy than dronedarone (CI=0.37-0.63, p<0.001). In terms of safety it was found that dronedarone had decreased odds of study drug termination (CI=1.13-39.3) and found that dronedarone's incidences of thyroid toxicity, symptomatic bradyarrhythmias, and hepatotoxicity were comparable to placebo. They also estimated that for every 1,000 patients treated with dronedarone, instead of amiodarone, there would be 228 more recurrences of AF at 1 year in exchange for 9.6 fewer deaths and 62 fewer adverse events

requiring discontinuation of drug (despite the fact that there was no statistically significant difference in death prevention found between the two drugs, $p=0.06$).

Head to Head Trial: DIONYSOS

Le Heuzey et al conducted a head to head trial with 504 amiodarone-naive patients who were randomized to receive dronedarone 400 mg twice daily ($n = 249$) or amiodarone 600 mg daily for 28 days followed by 200 mg daily ($n = 255$) for at least 6 months.¹³ The primary composite endpoint was recurrence of AF (including unsuccessful electrical cardioversion, no spontaneous conversion and no electrical cardioversion) or premature study discontinuation (due to intolerance or lack of efficacy). The main safety endpoint (MSE) was occurrence of thyroid, hepatic, pulmonary, neurologic, skin, eye, or gastrointestinal adverse events, or premature study drug discontinuation following an adverse event. Amiodarone was found to be more efficacious than dronedarone in terms of preventing AF recurrence or premature drug discontinuation due to intolerance or lack of efficacy (55.8% vs. 75.1% respectively, $p<0.0001$). The MSE for amiodarone compared to dronedarone was 44.5% vs. 39.5% ($p=0.129$) at 12 months. However, when GI events were excluded from the analysis (dronedarone had higher rates of nausea, vomiting, and diarrhea) there was a statistically significant reduction in MSE in the dronedarone group (RRR of 39%, $p=0.002$). Fewer patients receiving dronedarone had decreases in heart rate resulting in bradycardia ($p=0.0067$). Amiodarone was found to have a statistically higher incidence of QT prolongation, neurologic adverse events and thyroid adverse events. Overall incidence of adverse events leading to permanent drug discontinuation was 12.9% in the dronedarone group and 17.6% amiodarone group (no p -value, CI, or RR provided to back the difference in percentage of permanent drug discontinuation). The amiodarone group also had a higher incidence of supratherapeutic INRs and hemorrhagic events ($p=0.03$) in relation to concurrent anticoagulation therapy.

ADVERSE EVENTS:⁵⁻⁶

Dronedarone

1-10%:

Gastrointestinal: Diarrhea (9%), nausea (5%), abdominal pain (4%), vomiting (2%), dyspeptic signs and symptoms (2%), dysgeusia (<1%)

General: Asthenic conditions (7%)

Cardiac: Bradycardia (3%)

Skin and Subcutaneous Tissue: Rashes (generalized, macular, maculopapular, erythematous), pruritis, eczema, dermatitis and dermatitis allergic (5%), photosensitivity reaction (<1%)

Laboratory Data/ECG Parameter Changes: Serum creatinine increased 10% or greater five days after initiation of treatment (51%), QTc prolongation (28%)

Amiodarone

Most Serious:

Pulmonary Toxicity (up to 10-17%, fatal in up to 10% of occurrences): Hypersensitivity pneumonitis or interstitial/alveolar pneumonitis

Exacerbation of Arrhythmia (2-5%)

Serious Liver Injury (has been fatal in a few cases)

10-33%:

Gastrointestinal: Nausea, vomiting

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4-9%:

Dermatologic: Solar dermatitis/photosensitivity

Neurologic: Malaise, fatigue, tremor/abnormal involuntary movements, lack of coordination, abnormal gait/ataxia, dizziness, paresthesias

Gastrointestinal: Constipation, anorexia

Ophthalmologic: Visual disturbances

Hepatic: Abnormal liver-function tests

Respiratory: Pulmonary inflammation or fibrosis

1-3%:

Thyroid: Hypothyroidism, hyperthyroidism

Neurologic: Decreased libido, insomnia, headache, sleep disturbances

Cardiovascular: Congestive heart failure, cardiac arrhythmias, SA node dysfunction

Gastrointestinal: Abdominal pain

Hepatic: Nonspecific hepatic disorders

Other: Flushing, abnormal taste and smell, edema, abnormal salivation, coagulation abnormalities

<1%:

Blue skin discoloration, rash, spontaneous ecchymosis, alopecia, hypotension, cardiac conduction abnormalities

PRECAUTIONS/CONTRAINDICATIONS:⁵⁻⁶

Dronedarone

Black Box Warning:

- NYHA Class IV heart failure or NYHA Class II-III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic

Contraindications:

- Second- or third- degree atrioventricular (AV) block or sick sinus syndrome (except when used in conjunction with a functioning pacemaker)
- Bradycardia <50 beats per minute
- Concomitant use of a strong CYP3A inhibitor
- Concomitant use of drugs or herbal products that prolong the QT interval and may induce Torsades de Pointes
- QTc Bazett interval ≥ 500 ms
- Severe hepatic impairment
- Pregnancy
- Nursing women

Warnings and Precautions:

- Heart failure: Consider suspending or discontinuing use if heart failure develops or worsens
- Hypokalemia and Hypomagnesemia: Maintain potassium and magnesium levels within the normal range
- QT prolongation: Discontinue use if QTc increases to ≥ 500 ms

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- Increase in creatinine: Causes a small increase in serum creatinine within a week of initiating use that does not reflect a change in underlying renal function
- Teratogenicity: Women of childbearing potential should use effective contraception

Amiodarone

Black Box Warning:

- Use in patients without the indicated life-threatening arrhythmias due to substantial toxicity

Contraindications:

- Cardiogenic shock
- Severe sinus-node dysfunction causing marked sinus bradycardia
- Second- or third-degree atrioventricular block
- If episodes of bradycardia have caused syncope, except when used in conjunction with a pacemaker
- Known hypersensitivity to the drug or to any of its components, including iodine
- Corneal refractive laser surgery contraindicated in most patients

Warnings and Precautions:

- Optic Neuropathy and/or neuritis
- Corneal Microdeposits: Appear in majority of adults on amiodarone but alone are not a reason to discontinue treatment
- Peripheral neuropathy
- Photosensitivity
- Thyroid abnormalities
- Elevated liver enzymes
- General anesthesia: Close monitoring is recommended
- Hypotension Post bypass: Rare occurrences of hypotension upon discontinuation of cardiopulmonary bypass during open-heart surgery
- Adult Respiratory Distress Syndrome (ARDS): Occurrences of ARDS have been reported postoperatively
- Thyroid tumors: Associated with a statistically significant, dose-related increased incidence in rats

LOOK-ALIKE/SOUND-ALIKE ERROR RISK POTENTIAL:¹⁴

Dronedarone: None identified to date

Amiodarone: Amantadine

FDA Risk Evaluation and Mitigation Strategy (REMS):¹⁵

Dronedarone: Medication guide and communication plan

-A medication guide must be given to patients with each dispensation of dronedarone

-A communication plan was implemented to educate health care professionals on risks associated with the use of Multaq®, the safe and appropriate prescribing information and the goals of the REMS

DRUG INTERACTIONS:⁵⁻⁷

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Dronedarone

- Antiarrhythmics: Avoid concomitant use
- Digoxin: Consider discontinuation or halve dose of digoxin before treatment and monitor
- Calcium channel blockers (CCB): Initiate CCB with low dose and increase after ECG verification of tolerability
- Beta-blockers: May provoke excessive bradycardia, initiate with low dose and increase after ECG verification of tolerability
- CYP3A inducers: Avoid concomitant use
- Grapefruit juice: Avoid concomitant use
- HMG-CoA reductase inhibitors (statins): Follow label recommendations for concomitant use of certain statins with CYP3A and P-glycoprotein inhibitors
- CYP3A substrates with a narrow therapeutic index (e.g. sirolimus and tacrolimus): Monitor and adjust dosage as needed

Amiodarone

- Protease inhibitors: May increase amiodarone concentrations, monitor for toxicity and concentrations
- Histamine H₁ antagonists: May cause QTc interval prolongation and torsades de pointes
- Histamine H₂ antagonists: May increase serum amiodarone levels
- Trazodone: May cause QTc interval prolongation and torsades de pointes
- Grapefruit juice: Should not be taken during treatment with oral amiodarone
- Cyclosporine: May increase cyclosporine levels resulting in elevated creatinine
- HMG-CoA reductase inhibitors (statins): May cause myopathy/rhabdomyolysis, consider use of lower starting and maintenance doses of statins
- Digoxin: On initiation of oral amiodarone, the need for digoxin therapy should be reviewed and the dose reduced by approximately 50% or discontinued, if concomitant use is continued monitor closely for toxicity
- Other antiarrhythmic agents (e.g. quinidine, procainamide, disopyramide, flecainide, phenytoin): Reserve concomitant use for patients with life-threatening ventricular arrhythmias who are incompletely responsive to a single agent or to amiodarone, use lower doses of other antiarrhythmic agents and monitor closely
- Antihypertensives (e.g. beta-blockers and calcium channel blockers): Possible potentiation of bradycardia, sinus arrest and AV block, hemodynamic and electrophysiologic interactions have also been observed
- Warfarin: Reduce warfarin dose by one-third to one-half and monitor prothrombin times closely
- Clopidogrel: May result in ineffective inhibition of platelet aggregation
- Rifampin: May decrease serum concentrations of amiodarone
- St. John's Wort: May decrease serum concentrations of amiodarone
- Fentanyl: May cause hypotension, bradycardia and decreased cardiac output
- Dextromethorphan: May increase serum concentrations of dextromethorphan
- Cholestyramine: May reduce serum levels and half-life of amiodarone
- Disopyramide: May cause QTc prolongation
- Fluoroquinolones, macrolide antibiotics and azoles: May cause QTc prolongation
- Lidocaine: May cause sinus bradycardia and seizures

- Use of oral amiodarone > 2 weeks impairs the metabolism of phenytoin, dextromethorphan and methotrexate
- Any potassium or magnesium deficiency should be corrected before instituting and during amiodarone therapy. Use caution when co-administering amiodarone with drugs which may induce hypokalemia and/or hypomagnesemia.

CONCLUSIONS:

While amiodarone has proven to be more efficacious than dronedarone in preventing the recurrence of AF, it carries with it a number of serious adverse reactions that dronedarone does not possess (including thyroid abnormalities, increases in LFTs, pulmonary fibrosis, and corneal microdeposits). Despite the fact that amiodarone is more effective in preventing AF, dronedarone may be considered preferable in certain low-risk patients (see Figure 1.). However, to date neither agent has been shown to have a mortality benefit.

RECOMMENDATIONS:

Based upon this information, it seems that amiodarone and dronedarone do not fit the usual NPTC criteria for inclusion on the NCF. While there still appears to be a place in therapy for these medications, it seems most reasonable to keep the decision a local one, rather than a national level decision. It also seems important to stress the importance of careful patient selection when utilizing these medications and following sound clinical judgment.

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