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VIEWPOINT AND COMMENTARY

Dronedarone for Atrial Fibrillation

Have We Expanded the Antiarrhythmic Armamentarium?

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Dronedarone is a new antiarrhythmic agent that was recently approved for the prevention of cardiovascular hospitalization driven by atrial fibrillation/flutter. Its approval was based largely on the results of the 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) trial, which demonstrated a significant 24% reduction in the combined end point of all-cause mortality and cardiovascular hospitalization, primarily driven by the latter. However, several other clinical trials have evaluated the impact of dronedarone on various cardiovascular end points and yielded mixed results. In this article, we summarize the available evidence concerning dronedarone, and offer practical recommendations to health care providers regarding its use in the treatment of atrial fibrillation. We conclude that the available data support the use of dronedarone in select patient populations as a second- or third-line agent. (J Am Coll Cardiol 2010;55:1569–76) © 2010 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common sustained arrhythmia in the U.S. (1), affecting nearly 2.3 million patients and accounting for one-third (400,000) of all patient discharges with arrhythmia as a principal diagnosis (2). The overall incidence of AF increases with each decade of age, affecting nearly 6% of people over age 65 years. Nearly 71,000 patients die each year from the complications of AF and atrial flutter (AFL) (2–4). Given the heavy burden of AF on morbidity, mortality, and health care resources, it is not surprising that the Institute of Medicine has listed treatment of AF at the top of 100 priorities for comparative effectiveness research as part of the American Recovery and Reinvestment Act (ARRA) of 2009 (5).

Management of patients with AF/AFL has focused on 2 therapeutic strategies: a "rhythm-control strategy," in which antiarrhythmic drugs are used along with electrical cardioversion when necessary to restore normal sinus rhythm, and a "rate-control strategy," in which no specific efforts are made to maintain sinus rhythm and slowing of the ventricular response rate is the main objective. Data from randomized controlled trials have failed to establish superiority of either strategy over the other while demonstrating the efficacy of both strategies in reducing symptoms and improving the quality of life (6,7). Reduced efficacy and increased toxicity of antiarrhythmic drugs likely contributed to the lack of benefit observed with rhythm control. Driven by these circumstances, substantial resources have been invested in the development of new agents that minimize toxicity while maintaining antiarrhythmic efficacy, and offer improved treatment options to patients in reducing morbidity and mortality associated with AF/AFL. It is in this context that the recent approval of dronedarone by the U.S. Food and Drug Administration (FDA) for the "prevention of cardiovascular hospitalization in patients with nonpermanent atrial fibrillation or atrial flutter" (8) has been enthusiastically received as having expanded the antiarrhythmic armamentarium (9). However, there are uncertainties with respect to the drug's efficacy and safety that merit careful scrutiny.

Dronedarone was specifically designed to overcome the side effects of its parent compound, amiodarone, while maintaining its antiarrhythmic efficacy. Although amiodarone has a longstanding track record for maintaining sinus rhythm, its use, particularly in higher doses, is limited by adverse side effects, especially thyroid and pulmonary toxicity. The electrophysiological properties of this new agent (10), which are similar to those of amiodarone, coupled with the absence of iodine in its molecule, which is thought to render the drug less toxic, raised expectations that the new drug might function as a safer alternative to amiodarone for the treatment of AF (11).

Dronedarone is well absorbed after oral administration, with a bioavailability of approximately 15% after extensive first pass metabolism. As with amiodarone, the drug is extensively metabolized primarily by cytochrome P-450 (CYP) 3A4 and excreted in the bile with minimal renal excretion (12). Thus, concurrent use of medications that

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Abbreviations and Acronyms

AF = atrial fibrillation
AFL = atrial flutter
bid = twice a day
CI = confidence interval
EF = ejection fraction
FDA = Food and Drug Administration
NYHA = New York Heart Association
RR = relative risk

inhibit CYP3A4 can increase exposure to the drug and result in potentially serious drug-drug interactions. Given that the drug is highly bound to plasma proteins, the steady-state terminal elimination half-life is approximately 30 h compared with the known long half-life of amiodarone (approximately 58 days) due to extensive tissue deposition (12). Like amiodarone, a 10% to 15% increase in serum creatinine can be seen with dronedarone; these changes are related to inhibition of tubular secretion of creatinine by the drug and do not represent a decrease in the glomerular filtration rate (12,13).

Several trials have investigated the efficacy and safety of dronedarone. Four trials evaluated the efficacy in delaying or reducing recurrence of AF/AFL (12,14,15), 1 assessed the impact on rate control (16), and 2 assessed morbidity and mortality outcomes (17,18) (Table 1). We herein review the evidence from these trials focusing on dronedarone's efficacy, safety, and tolerability, and provide recommendations for its optimal use in clinical practice.

Antiarrhythmic Efficacy of Dronedarone

The antiarrhythmic efficacy of dronedarone has been evaluated in 4 placebo-controlled and 1 active-control randomized trials.

Delay in recurrences of AF or maintenance of sinus rhythm. Data regarding the antiarrhythmic efficacy of dronedarone are summarized in Table 2. The DAFNE (Dronedarone Atrial Fibrillation Study After Electrical Cardioversion) study was a phase 2 dose-ranging study that established a 400 mg twice daily dose to have optimal efficacy and safety (14). The EURIDIS (European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm) and ADONIS (American-Australian Trial With Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm) studies were identical sister trials performed under the same protocol that assessed the efficacy of dronedarone to maintain sinus rhythm in patients with a history of nonpermanent AF/AFL who were in sinus rhythm at the time of randomization and had no clinically significant structural heart disease or heart failure (15). Pooled data from these 2 studies demonstrated that at 12 months, 64% of dronedarone-treated patients were estimated (Kaplan-Meier) to have experienced a first AF/AFL recurrence, compared with 75% of placebo-treated patients ($p < 0.001$). Data for symptomatic recurrence were 38% with dronedarone and 46% with placebo ($p = 0.0003$) (15). Although the 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) study was designed to primarily evaluate the impact of dronedarone on clinical outcomes, data on arrhythmia recurrence were also assessed. In all 4 trials, dronedarone delayed the time to the first recurrence of arrhythmia and decreased recurrence of these events. Pooled data from all 4 studies are shown in Figure 1 and demonstrate that 43% of dronedarone-treated patients were estimated to have experienced a first AF/AFL recurrence, compared with 54% of placebo-treated patients (an absolute risk difference of 11%; number needed to treat = 9; $p < 0.0001$).

To put these findings into perspective, dronedarone is not much more effective than quinidine (50% efficacy in maintaining sinus rhythm compared with 25% for placebo at 1 year) (19). In contrast, a recent meta-analysis of 11 studies involving a total of 5,044 patients reported a threefold greater improvement in achieving and maintaining sinus rhythm with amiodarone compared with a placebo or rate-control drug (20). Moreover, previous studies with sotalol and amiodarone have demonstrated attenuation of treatment effect with longer follow-up (21–23). There is no evidence to suggest that this might not be the case with dronedarone as well. Thus, these data suggest that dronedarone has modest antiarrhythmic efficacy.

Table 1 Summary of Dronedarone Trials

Trial Name	Dose	Population Studied	Mean Follow-Up	Primary Efficacy End Point
DAFNE (n = 142)	Dronedarone 400 to 800 mg bid vs. placebo	Nonpermanent AF/AFL (low risk)	6 months	Time to recurrence of AF/AFL
EURIDIS (n = 612)	Dronedarone 400 mg bid vs. placebo	Nonpermanent AF/AFL (low risk)	12 months	Time to recurrence of AF/AFL
ADONIS (n = 625)	Dronedarone 400 mg bid vs. placebo	Nonpermanent AF/AFL (low risk)	12 months	Time to recurrence of AF/AFL
ERATO (n = 174)	Dronedarone 400 mg bid vs. placebo	Permanent AF (low risk)	6 months	Rate control
ANDROMEDA (n = 627)	Dronedarone 400 mg bid vs. placebo	Worsening CHF (high risk)	13 months	ACM or CHF hospitalization
ATHENA (n = 4,628)	Dronedarone 400 mg bid vs. placebo	Stable (low to moderate risk)	21 months	ACM or CV hospitalization
DIONYSOS (n = 504)	Dronedarone 400 mg bid vs. amiodarone 200 mg	Nonpermanent AF/AFL	6 months	Recurrence of AF/AFL or discontinuation due to intolerance

ACM = all-cause mortality; ADONIS = American-Australian Trial With Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm; AF = atrial fibrillation; AFL = atrial flutter; ANDROMEDA = Antiarrhythmic Trial With Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease; 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; bid = twice a day; CHF = congestive heart failure; CV = cardiovascular; DAFNE = Dronedarone Atrial Fibrillation Study After Electrical Cardioversion; DIONYSOS = Efficacy and Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation); ERATO = Efficacy and Safety of Dronedarone for the Control of Ventricular Rate During Atrial Fibrillation; EURIDIS = European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm.