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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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) 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 in 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

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Dose</th>
<th>Population Studied</th>
<th>Mean Follow-Up</th>
<th>Primary Efficacy End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAFNE (n = 142)</td>
<td>Dronedarone 400 to 800 mg bid vs. placebo</td>
<td>Nonpermanent AF/AFL (low risk)</td>
<td>6 months</td>
<td>Time to recurrence of AF/AFL</td>
</tr>
<tr>
<td>EURIDIS (n = 612)</td>
<td>Dronedarone 400 mg bid vs. placebo</td>
<td>Nonpermanent AF/AFL (low risk)</td>
<td>12 months</td>
<td>Time to recurrence of AF/AFL</td>
</tr>
<tr>
<td>ADONIS (n = 625)</td>
<td>Dronedarone 400 mg bid vs. placebo</td>
<td>Nonpermanent AF/AFL (low risk)</td>
<td>12 months</td>
<td>Time to recurrence of AF/AFL</td>
</tr>
<tr>
<td>ERATO (n = 174)</td>
<td>Dronedarone 400 mg bid vs. placebo</td>
<td>Permanent AF (low risk)</td>
<td>6 months</td>
<td>Rate control</td>
</tr>
<tr>
<td>ANDROMEDA (n = 627)</td>
<td>Dronedarone 400 mg bid vs. placebo</td>
<td>Worsening CHF (high risk)</td>
<td>13 months</td>
<td>ACM or CHF hospitalization</td>
</tr>
<tr>
<td>ATHENA (n = 4,628)</td>
<td>Dronedarone 400 mg bid vs. placebo</td>
<td>Stable (low to moderate risk)</td>
<td>21 months</td>
<td>ACM or CV hospitalization</td>
</tr>
<tr>
<td>DIONYSOS (n = 504)</td>
<td>Dronedarone 400 mg bid vs. amiodarone 200 mg</td>
<td>Nonpermanent AF/AFL</td>
<td>6 months</td>
<td>Recurrence of AF/AFL or discontinuation due to intolerance</td>
</tr>
</tbody>
</table>
The DIONYSOS (Efficacy and Safety of Dronedarone Versus Amiodarone for the Maintenance of Sinus Rhythm in Patients With Atrial Fibrillation) trial compared the efficacy and safety of dronedarone (400 mg twice a day [bid]) versus amiodarone (600 mg daily for 28 days, then 200 mg daily thereafter) for at least 6 months for the maintenance of sinus rhythm in patients with AF (12). The primary composite end point of AF recurrence or premature drug discontinuation was reached in 74% of patients taking dronedarone versus 55% of patients receiving amiodarone (p < 0.001) (12). Description of the components of the primary end point showed that recurrences of AF were more frequent in the dronedarone group than in the amiodarone group (63% vs. 42%; relative risk [RR]: 1.51, 95% confidence interval [CI]: 1.27 to 1.80) (Table 2), whereas premature study drug discontinuations due to intolerance were less frequent in the dronedarone group (10.4% vs. 13.3%; RR: 0.78, 95% CI: 0.48 to 1.27 (24). Thus, dronedarone had a statistically significant 50% reduced efficacy in maintaining sinus rhythm (37% vs. 58%), while only being modestly, but not significantly, better tolerated than amiodarone (22% risk reduction).

**Rate control.** The ERATO (Efficacy and Safety of Dronedarone for the Control of Ventricular Rate During Atrial Fibrillation) trial was a placebo-controlled study to evaluate the efficacy of dronedarone 400 mg bid given for 6 months in controlling the ventricular rate in patients with symptomatic permanent AF at rest (16). The primary end point, decrease from baseline in 24-h Holter heart rate on day 14, was significantly more pronounced in the dronedarone group (37% vs. 58%) (16). The control arm in all trials was placebo except for the DIONYSOS study, where dronedarone was compared with amiodarone. Abbreviations as in Table 1.

### Table 2 Antiarrhythmic Efficacy of Dronedarone

<table>
<thead>
<tr>
<th>Study</th>
<th>Dronedarone</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAFNE</td>
<td>35/54 (65%)</td>
<td>43/48</td>
<td>0.45 (0.28–0.72)</td>
<td>0.001</td>
</tr>
<tr>
<td>Recurrence rate</td>
<td>35/54 (65%)</td>
<td>43/48</td>
<td>0.72 (0.58–0.90)</td>
<td>0.004</td>
</tr>
<tr>
<td>EURIDIS</td>
<td>96</td>
<td>41</td>
<td>0.78 (0.64–0.96)</td>
<td>0.013</td>
</tr>
<tr>
<td>Recurrence rate</td>
<td>150/411 (37%)</td>
<td>95/201 (47%)</td>
<td>0.77 (0.64–0.94)</td>
<td>0.009</td>
</tr>
<tr>
<td>ADONIS</td>
<td>158</td>
<td>59</td>
<td>0.73 (0.59–0.89)</td>
<td>0.002</td>
</tr>
<tr>
<td>Recurrence rate</td>
<td>154/417 (37%)</td>
<td>89/208 (43%)</td>
<td>0.86 (0.71–1.06)</td>
<td>0.151</td>
</tr>
<tr>
<td>ATHENA</td>
<td>498</td>
<td>737</td>
<td>0.75 (0.65–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrence rate</td>
<td>779/1,732 (45%)</td>
<td>950/1,741 (55%)</td>
<td>0.75 (0.68–0.82)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Dronedarone dose 400 mg twice a day; time to recurrence is shown in median days. The control arm in all trials was placebo except for the DIONYSOS study, where dronedarone was compared with amiodarone. Abbreviations as in Table 1.

**Figure 1 RR of AF Recurrence With Dronedarone Versus Placebo**

In a meta-analysis of relative risk of recurrence of atrial fibrillation (AF) treated with dronedarone compared with placebo, a fixed effects (FE) Mantel-Haenszel model was used for pooling the data. Heterogeneity was assessed by Cochran’s Q and I² tests. The diamond shows the summary relative risk (RR) centered on a combined estimate and extending to 95% confidence intervals (CIs). The squares and horizontal lines indicate RR and 95% CIs, respectively, for individual studies. The size of the squares is proportional to the weight of each study in the meta-analysis. See Table 1 for trial acronym definitions.
group (mean of 86.5 to 76.2 beats/min) than in the placebo group (90.6 to 90.2 beats/min) (16). This rate-controlling effect of dronedarone was sustained throughout the 6-month trial and was additive to the effect of other rate-control therapies. A similar pattern was seen among patients with AF recurrence in the DAFNE trial, where the mean ventricular rate was lower with dronedarone 400 mg bid (89.7 vs. 102.9 beats/min, \( p < 0.001 \)) (14), the EURIDIS and ADONIS trials (102 vs. 117 beats/min, \( p < 0.001 \)) (15), and the ATHENA trial (75 vs. 84 beats/min, \( p < 0.001 \)) (18). These findings demonstrate that dronedarone reduces the ventricular rate of patients with both permanent and nonpermanent AF.

Thus, in aggregate, these studies establish that dronedarone has the ability to control both rhythm and rate in patients with AF/AFL. However, the antiarrhythmic efficacy is quite modest compared with placebo and only half as effective compared with the gold standard amiodarone.

**Safety of Dronedarone**

The safety of dronedarone has been evaluated in 2 randomized controlled trials. The ANDROMEDA (Antiarrhythmic Trial With Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease) study was designed to establish the safety in a vulnerable (high-risk) population, whereas the ATHENA trial was performed to define a population for which dronedarone may be safely used.

The ANDROMEDA trial enrolled patients with recently symptomatic decompensated heart failure (New York Heart Association [NYHA] functional class II to IV) who may or may not have had AF (17). Approximately 25% and 37% of patients enrolled had AF on randomization or a history of AF, respectively. The primary end point was time to mortality or hospitalization for worsening heart failure. The trial was terminated prematurely after 650 (627 evaluable cases) of a planned 1,000 were enrolled because of excess mortality among dronedarone-treated patients (17). The excess mortality appeared to be predominantly related to worsening heart failure, followed by arrhythmia and sudden death. The reason for excess mortality has been the subject of debate. Possible explanations include the following: 1) a chance finding due to uncertainty related to premature stopping of the trial; 2) a true finding related to a deleterious effect of dronedarone—mediated by its negative inotropic effect secondary to sodium-channel blockade, beta-blockade, or adenylylcytase inhibition—in recently unstable patients hospitalized for decompensated heart failure; or 3) increased mortality due to inappropriate discontinuation of angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker as a result of dronedarone-induced inhibition of creatinine secretion. The latter is unlikely, given that the relative risk of death among patients who never took or interrupted these medications appeared to be higher (2 of 36 vs. 15 of 61; RR: 5.1, 95% CI: 1.16 to 22.2) compared with the overall ANDROMEDA study population (RR: 2.3, 95% CI: 1.1 to 4.2) (12). The most plausible explanation relates to the instability of patients enrolled in the ANDROMEDA trial. The outcome of the ANDROMEDA study resulted in a nonapproval recommendation by the FDA, which indicated that approval could be reconsidered if efficacy and safety could be demonstrated in a different and defined population.

The ATHENA study was a randomized trial to evaluate the long-term effect of dronedarone 400 mg bid versus placebo on the combined risk of cardiovascular hospitalization or all-cause mortality in patients with a recent or current history of nonpermanent AF/AFL and additional risk factors (18). The trial included 4,628 patients (making it the largest antiarrhythmic trial ever conducted) with >85% with history of hypertension, 60% with structural heart disease, and 31% with coronary artery disease. Although patients with stable heart failure were included, the trial excluded patients who were clinically decompensated—only 21% of patients had NYHA functional class II or III heart failure (none had class IV heart failure) and only 4% had left ventricular ejection fraction (EF) <0.35 compared with 100% of patients who had class II or greater heart failure in the ANDROMEDA study. Treatment with dronedarone was associated with a 24% reduction of the combined risk of cardiovascular hospitalization or all-cause death (RR: 0.76, 95% CI: 0.69 to 0.84) compared with placebo over a follow-up of 21 months (18). Based largely on the results of the ATHENA study, the FDA approved dronedarone to reduce the risk of cardiovascular hospitalization in the treatment of AF/AFL.

There are several points regarding the ATHENA study that merit consideration. First, although it was 1 of the few antiarrhythmic trials to focus on hard clinical end points, the combined primary end point was primarily driven by cardiovascular hospitalization, mostly related to AF or any supraventricular arrhythmia. All-cause mortality was not statistically different (RR: 0.84, 95% CI: 0.66 to 1.08). The upper bound of 1.08 indicates that a meaningful, namely, >8%, increase in the risk of death associated with dronedarone was excluded. However, subgroup analysis revealed that the only subgroup for whom a clinically meaningful increase in the risk of death was excluded was the clinically stable patients without AF/AFL on randomization (the majority of patients enrolled in ATHENA), with a hazard ratio of 0.81 (95% CI: 0.61 to 1.09). The upper bound of the confidence interval was 1.21 for patients with EF <35% (0.55 [95% CI: 0.25 to 1.21]), 1.34 in patients with NYHA functional class III heart failure (0.66 [95% CI: 0.32 to 1.34]), 1.47 in patients with NYHA class I or II heart failure (0.93 [95% CI: 0.59 to 1.47]), and 1.51 in stable patients with AF/AFL on randomization, indicating that an increase in mortality ranging from as high 21% to 51% could not be excluded in these patients (12,18). Taken together with the findings of the ANDROMEDA trial, these observations suggest that caution is warranted in considering dronedarone for patients who have heart failure in
general, and that the use of dronedarone in patients with NYHA functional class IV heart failure or NYHA class II or III heart failure with recently decompensated heart failure is contraindicated, resulting in a boxed warning by the FDA (24).

Second, it is unclear why patients were hospitalized for AF, a key point relevant to clinical practice. Unlike the ANDROMEDA trial, the end points (including hospitalizations) were not adjudicated by an external committee but were reported by the investigators. The information in the investigator’s case report forms was incomplete and it did not capture whether patients were symptomatic, hemodynamically unstable, had exacerbation of heart failure, or required anticoagulation therapy, all common indications for hospitalizations for AF (12). Given that dronedarone has a modest effect on AF recurrence and heart rate control, it is unlikely that these would primarily account for reduced hospitalizations. It is interesting to note that the favorable trend in reduced heart failure hospitalizations with dronedarone was not accompanied by symptomatic benefit in fatigue, dyspnea, and peripheral edema (12). That may well be due to incomplete capture of information in the case report forms. Furthermore, dronedarone had no impact on quality of life (as assessed by a survey tool)—an expected beneficial outcome of reduced hospitalizations. However, this was not systematically or properly evaluated during the entire course of the trial (12). Nonetheless, these observations raise questions about the quality of the data in the ATHENA study and cast doubts on their relevance to clinical practice. Conversely, if reliably replicated in clinical practice, the potential reduction in cardiovascular hospitalizations, especially the intensive care unit admissions, might have the potential for cost savings. However, at a retail cost of $9 per day ($4.50 per 400 mg dose) or $3,285 per year, it remains to be seen whether it will be cost effective compared with generic amiodarone.

Third, the quality of the data regarding cardiovascular death—a secondary end point that favored dronedarone (RR: 0.70, p = 0.037)—is suspect. The secondary end points were arranged to be analyzed sequentially. The first secondary end point was all-cause mortality, which as noted in the preceding text, was not significantly lower with dronedarone, which arguably precludes evaluation of subsequent end points of cardiovascular death (or cardiovascular hospitalization alone). The finding that the p value for cardiovascular death changed from being “not significant”—0.75 (95% CI: 0.54 to 1.04)—at a planned enrollment of 4,300 to being “significant”—0.71 (95% CI: 0.51 to 0.98)—at extended enrollment of 4,637 warrants scrutiny (25). Moreover, lack of adjudication of events might introduce unreliability in the classification of the cause of death. Given these limitations, it is not surprising that the FDA did not allow a claim for cardiovascular or all-cause mortality in favor of dronedarone as originally proposed by the sponsor (24).

Pooled analysis of morbidity and mortality. Pooled analysis of 6 dronedarone trials involving a total of 6,771 patients yielded no significant differences in the incidence of all-cause mortality or cardiovascular hospitalization compared with placebo (Fig. 2A). There was significant statistical as well as clinical heterogeneity, mostly attributable to the ANDROMEDA trial, which recruited high-risk patients with recently decompensated heart failure. Accordingly, in a sensitivity analysis that excludes the results of the ANDROMEDA study, use of dronedarone was associated with a 20% lower risk of the combined outcome (RR: 0.80, 95% CI: 0.74 to 0.86, heterogeneity p = 0.09). Similarly, combining data from all 6 trials, the pooled estimates for all-cause mortality revealed a nonsignificant 5% decrease in risk with dronedarone (Fig. 2B) (26). The upper bound of 1.18 means that up to an 18% increase in mortality could not be excluded with dronedarone. The pooled estimate excluding the ANDROMEDA trial yielded an RR of 0.85 (95% CI: 0.68 to 1.07), thereby excluding up to a >7% increase in the risk of death with dronedarone. Thus, these data provide reassurance that dronedarone use is likely to be safe for low-intermediate risk stable patients, namely, those without recently decompensated heart failure or severe left ventricular dysfunction.

Adverse Event Profile

The safety and tolerability of dronedarone has been well characterized in >3,200 patients with a mean follow-up of approximately 12 months. The main clinical adverse events identified with dronedarone are diarrhea, nausea or vomiting, and rash. Dronedarone produces electrocardiographic changes consistent with its pharmacodynamic activity; there is no evidence of a proarrhythmic effect of dronedarone, with only 1 case of torsades de pointes identified so far. There is no deleterious impact on oral anticoagulation therapy management. A benign transient increase in serum creatinine (attributed to inhibition of renal tubular secretion) has been observed with dronedarone that peaks at 7 days and returns to baseline within 1 week after treatment discontinuation (15). Unlike amiodarone, dronedarone is not associated with endocrinological, neurological, or pulmonary toxicity in the pooled AF/AFL studies, although a mean follow-up of 12 months (21 months in the ATHENA study) may be an insufficient duration for observing the type of pulmonary toxic effects seen with long-term amiodarone use.

In the DIONYSOS study, which compared 400 mg bid dronedarone with 200 mg amiodarone, dronedarone was associated with a reduced risk of thyroid disorders, sleep disorders, and tremor, and fewer episodes of bleeding due to less interference with oral anticoagulants, but the risk of adverse gastrointestinal events was increased. However, premature discontinuations due to treatment-related adverse events (the primary tolerability end point) were not statistically different—10.4% versus 13.3% (RR: 0.78, 95% CI: 0.48 to 1.27) (12). Although no pulmonary or liver toxic effects were seen with either agent, the short duration (6
(months) of the study precludes any definitive conclusions regarding long-term safety. Thus, while dronedarone has been shown to be well tolerated compared with placebo, when compared with amiodarone, it has a modest, but nonsignificant, tolerability advantage. Long-term studies are required to conclusively establish the superior safety and tolerability of dronedarone over amiodarone.

**Conclusions and Implications**

The emergence of a new antiarrhythmic drug for AF/AFL has been long awaited after the approval of dofetilide nearly a decade back (27). It is, therefore, no surprise that a great deal of anticipation has surrounded the approval of dronedarone. Envisioned as a safer alternative to amiodarone for maintaining sinus rhythm in patients with AF, dronedarone may also lower the risk of some clinical outcomes. However, its relatively modest efficacy in preventing AF/AFL recurrence or rate control as well as questions regarding its short- and long-term safety in at-risk patients leave its role in the management of this arrhythmia uncertain.

What role do we see for this drug in clinical practice? In general, based on available evidence, it is difficult to support an approach to rhythm control in most patients with AF without first trying a rate-control strategy. Treatment with antiarrhythmic drugs should generally be considered only when symptoms persist despite adequate rate control. When a rhythm-control strategy is desired for patients with no or minimal heart disease, including patients with hypertension.
but without substantial left ventricular hypertrophy, flecainide, propafenone, and sotalol are recommended as first-line agents by guidelines (28) based on their proven safety and efficacy in this population (Fig. 3). The use of dronedarone might merit consideration for these patients as an alternative to amiodarone or dofetilide (recommended as second-line agents), especially for patients intolerant to these drugs. For patients with hypertension and substantial left ventricular hypertrophy, amiodarone should be used as first-line treatment (28) with consideration for dronedarone only for patients who are intolerant of amiodarone. For patients with coronary artery disease and without overt heart failure, for whom dofetilide and sotalol are recommended as first-line treatment option (28), dronedarone might be a reasonable alternative to these drugs or to amiodarone (second-line therapy). Among patients with heart failure (representing a sizeable group with this arrhythmia) for whom a rhythm-control strategy is desired, amiodarone or dofetilide is recommended as a first-line agent based on its neutral effect on survival in these patients. In general, dronedarone should be avoided in patients with heart failure, especially those with advanced or recently decompensated heart failure (more than NYHA functional class II, or EF ≤35% [ANDROMEDA-type patients]) for which it carries a "boxed" warning. However, for patients with less advanced and without recently (within the last month) decompensated heart failure (NYHA functional class II or less, or EF >35% [ATHENA-type patients]), dronedarone could potentially offer a reasonable alternative, particularly for patients who are intolerant of low-dose amiodarone or dofetilide. For patients falling between the ANDROMEDA and ATHENA study populations, the benefit-risk profile of dronedarone is unclear. Thus, the available data support only limited use of dronedarone for select patient populations, mostly as a second- or third-line agent in lieu of amiodarone.

Although the drug has been approved to reduce cardiovascular hospitalizations related to AF/AFL in a restricted patient population (low-intermediate risk patients with current or previous history of nonpermanent AF/AFL but without advanced or recently decompensated heart failure), we anticipate that, in clinical practice, it will likely be used...
for a broader population and for indications beyond its approved label. Although we recognize that reconciling efficacy versus safety is ultimately a matter of clinical judgment and patient preference, we nevertheless caution against the indiscriminate use of dronedarone. To further understand how dronedarone will fare against amiodarone in the wider population with heart disease, more studies with longer follow-up are needed. At the very least, these studies need to demonstrate superior tolerability of dronedarone without unacceptable loss of efficacy in the maintenance of sinus rhythm and quality of life, or without an increase in morbidity or mortality compared with amiodarone. Until then, dronedarone may be best viewed only as half a step forward in our efforts to expand the antiarrhythmic armamentarium.

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REFERENCES


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