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## Dronedarone

Chinmay Patel, MD; Gan-Xin Yan, PhD; Peter R. Kowey, MD

**Abstract**—Amiodarone is the most effective antiarrhythmic drug for maintaining sinus rhythm for patients with atrial fibrillation. Extra-cardiac side effects have been a limiting factor, especially during chronic use, and may offset its benefits. Dronedarone is a noniodinated benzofuran derivative of amiodarone that has been developed for the treatment of atrial fibrillation and atrial flutter. Similar to amiodarone, dronedarone is a potent blocker of multiple ion currents, including the rapidly activating delayed-rectifier potassium current, the slowly activating delayed-rectifier potassium current, the inward rectifier potassium current, the acetylcholine activated potassium current, peak sodium current, and L-type calcium current, and exhibits antiadrenergic effects. It has been studied for maintenance of sinus rhythm and control of ventricular response during episodes of atrial fibrillation. Dronedarone reduces mortality and morbidity in patients with high-risk atrial fibrillation, but may be unsafe in those with severe heart failure. This article will review evidence of safety and effectiveness of dronedarone in patients with atrial fibrillation. (*Circulation*. 2009;120:636-644.)

**Key Words:** amiodarone ■ arrhythmia ■ atrial fibrillations ■ dronedarone

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and a usual cause for hospitalization and consultation.<sup>1,2</sup> It is an epidemic. It is projected that by 2050, more than 15 million people will contract AF in the United States alone.<sup>2,3</sup> Nearly 1 in every 10 persons aged 80 years and older has AF,<sup>1,4,5</sup> predisposing them to stroke, heart failure, and death.<sup>6,7</sup> A recent report from *Centers for Medicare and Medicaid Services* suggested that AF accounted for 1 765 304 hospitalizations in 1999.<sup>8</sup> The cost of medical care for patients with AF is almost 5 times higher than the care of patients without AF.<sup>9,10</sup> Despite improvements in primary and secondary prevention of ischemic heart disease and hypertension, the US age-adjusted death rate due to AF increased from 27.6 in 1980 to 69.8 per 100 000 in 1998.<sup>2,11</sup>

Current therapy for AF is multidimensional and complicated.<sup>12</sup> There is some consensus on the benefits of anticoagulation in patients with AF, but debate continues about the relative value of rate versus rhythm control. Recent clinical trials have failed to demonstrate superiority of sinus rhythm maintenance,<sup>13–18</sup> but antiarrhythmic therapy is important for patients with severe symptoms. Conventional antiarrhythmic drugs have limited efficacy and safety. In fact, data suggest that the benefit of restoring and maintaining sinus rhythm in AF may be offset by significant cardiac and extracardiac side effects of currently used drugs.<sup>19–21</sup> Improvement in the current approach to AF is clearly necessary. This review focuses on dronedarone, a new antiarrhythmic drug for AF suppression (Figure 1).

### Electrophysiological Properties of Dronedarone

#### In Vitro Experiments

In vitro electrophysiological properties of dronedarone and its comparison with amiodarone are summarized in Table 1.<sup>23–33</sup> In patch clamp experiments using human atrial myocytes, 3  $\mu\text{mol/L}$  of dronedarone produced potent blockade of peak sodium current, an effect 10-fold greater than that of an equal concentration of amiodarone.<sup>23</sup> In guinea pig ventricular myocytes, dronedarone inhibited the rapidly activating delayed-rectifier potassium current, the slowly activating delayed-rectifier potassium current, the inward rectifier potassium current, and L-type calcium current.<sup>24</sup> Additionally, dronedarone exhibited strong inhibitory effects on the acetylcholine-activated potassium current ( $I_{K\text{-Ach}}$ ) in rabbit sinoatrial nodal cells<sup>32</sup> and guinea pig atrial cells.<sup>31</sup> Blockade of  $I_{K\text{-Ach}}$  by dronedarone was 100 times more potent than that of amiodarone.<sup>31</sup> A potent  $I_{K\text{-Ach}}$  blocking property is of additional therapeutic value especially for treatment of AF, because  $I_{K\text{-Ach}}$  plays a prominent role in vagally induced AF and has been shown to be constitutively active in chronic AF.<sup>34,35</sup>

Like amiodarone, dronedarone exerts its antiadrenergic effects by noncompetitive binding to  $\beta$ -adrenergic receptors and inhibition of agonist-induced increases in adenylate cyclase activity.<sup>33</sup> Dronedarone (0.01 to 1  $\mu\text{mol/L}$ ) induced a concentration-dependent reduction of coronary perfusion pressure in isolated guinea pig hearts, effects that were independent of the nitric oxide synthase pathway and possibly related to its calcium current blockade.<sup>36</sup>

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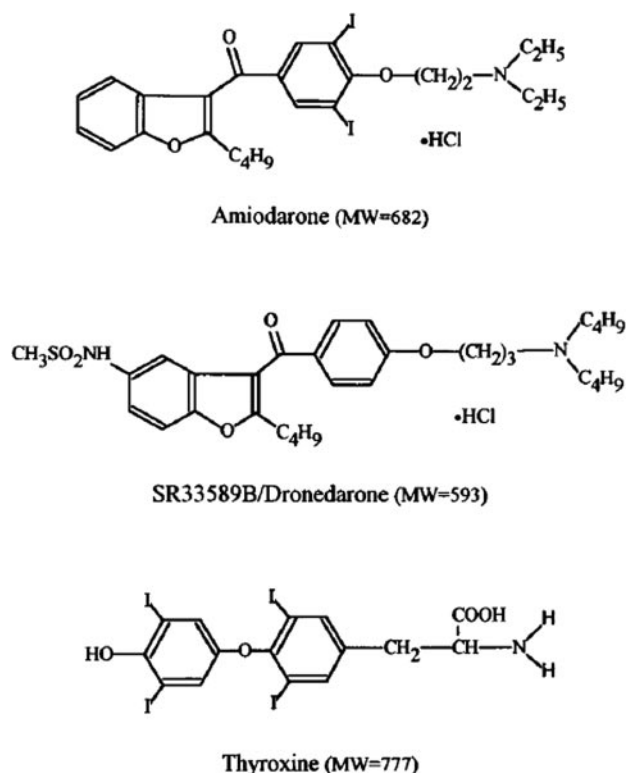
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**Figure 1.** Molecular structure of amiodarone, dronedaronne, and thyroxine. As compared with amiodarone, in the dronedaronne molecule, ethyl groups on the terminal nitrogen are replaced by butyls groups, the iodine moiety is removed, and a methanesulfonyl group has been added to benzofuran ring. Reproduced from Sun et al<sup>22</sup> with permission from the publisher. Copyright © 1999, the American Heart Association.

The effect of dronedaronne on single-cell cardiac action potential is variable, depending on species and the duration of drug administration. The most consistent effect is use-dependent inhibition of maximum upstroke velocity, both after acute and sustained administration. Acute administration of 0.1 to 10  $\mu\text{mol/L}$  of dronedaronne decreased action potential duration in rabbit papillary muscle,<sup>22</sup> rabbit atrial muscle,<sup>37</sup> and the canine papillary muscle preparation,<sup>25</sup> with no effect on guinea pig ventricular myocytes.<sup>24</sup> On the other hand, sustained administration of drug increased action potential duration in rabbit papillary muscles<sup>22</sup> and rabbit atrial muscles.<sup>37</sup> The action potential duration of dog papillary muscle remained unchanged.<sup>25</sup> In canine left ventricular Purkinje fibers, 10  $\mu\text{mol/L}$  of dronedaronne reduced the incidence of early and delayed afterdepolarizations evoked by dofetilide and ouabain, respectively.<sup>25</sup> Similarly, dronedaronne reduced transmural dispersion of repolarization and abolished d-sotalol-induced early afterdepolarizations in canine left ventricular tissue slices.<sup>38</sup>

Thus dronedaronne has multichannel blocking properties comparable to those of amiodarone. It is a more potent blocker of peak sodium current and  $I_{K\text{-ACh}}$  currents and has stronger in vitro antiadrenergic effects compared with amiodarone.

### In Vivo Experiments

As with amiodarone, the effects of dronedaronne on ventricular repolarization depend on duration of drug administration

and species. Although acute administration of dronedaronne abbreviates repolarization,<sup>39</sup> sustained administration increases the QTc interval.<sup>40</sup> The difference in electrophysiological effects between acute versus sustained administration may be partially due to the fact that dronedaronne and amiodarone are highly protein-bound in vivo.<sup>41,42</sup> Therefore, it is difficult to directly extrapolate in vitro effects of dronedaronne to its in vivo actions.

In dogs with complete atrioventricular block, intravenous administration of dronedaronne shortened ventricular action potential duration and suppressed alkalinant-induced early afterdepolarization, ectopic beats, and torsade de pointes.<sup>39</sup> Sustained administration of dronedaronne 20 mg/kg twice a day for 4 weeks increased the QTc interval by 31% in the same in vivo model.<sup>40</sup> Similarly, sustained administration of 50 mg/kg per day of dronedaronne for 4 weeks in rabbits significantly prolonged the QT and R-R intervals and reduced sinoatrial nodal automaticity.<sup>22</sup> In contrast, chronic dronedaronne treatment in the same dose in normal dogs did not lengthen the QT interval significantly.<sup>25</sup>

In the rat model of ischemia and reperfusion-induced arrhythmias, intravenous dronedaronne, but not amiodarone, prevented ventricular fibrillation.<sup>43</sup> Similar findings were reported in anesthetized pigs in which dronedaronne proved more potent than amiodarone in inhibiting ischemia-induced ventricular arrhythmias.<sup>44</sup>

Studies in conscious and anesthetized dogs have shown that dronedaronne displays potent antiadrenergic activity, similar to that of amiodarone.<sup>45,46</sup> In conscious dogs with healed myocardial infarctions, pretreatment with dronedaronne reduced resting heart rate without compromising left ventricular function. Dronedaronne was as effective as amiodarone in reducing exercise- and isoprenaline-induced tachycardia.<sup>45</sup>

### Pharmacokinetics

Dronedaronne is well absorbed ( $\approx 70\%$  to  $94\%$ ) after oral administration, and absorption increases 2- to 3-fold when it is taken with food. Dronedaronne undergoes significant first-pass metabolism that reduces its net bioavailability to 15%. With sustained administration of 400 mg twice daily, steady-state plasma concentrations of 84 to 167 ng/mL are reached in 7 days.<sup>41</sup> The clearance of dronedaronne is principally nonrenal, with a terminal half-life of  $\approx 24$  hours.

Dronedaronne is a substrate for and a moderate inhibitor of CYP3A4.<sup>41</sup> A potent CYP3A4 inhibitor such as ketoconazole may increase dronedaronne exposure by as much as 25-fold. Consequently, dronedaronne should not be coadministered with potent CYP3A4 inhibitors like antifungals, macrolide antibiotics, or protease inhibitors. When coadministered with moderate CYP3A4 inhibitors such as verapamil and diltiazem, lower doses of concomitant drugs should be used to avoid severe bradycardia and conduction block.<sup>41</sup>

Concomitant administration of dronedaronne and digoxin results in a 1.7- to 2.5-fold increase in serum digoxin concentration, likely due to a P-glycoprotein-mediated interaction in the kidney.<sup>41</sup> This necessitates frequent monitoring of digoxin concentration and possible dose reduction. Co-administration of dronedaronne and simvastatin, a CYP3A4

**Table 1. Ion Channel Effects of Dronedarone and Its Comparison With Amiodarone**

Current	Tissue	Dronedarone	Amiodarone	Comments
$I_{Na}$	Human atrial myocytes	97% block at 3 $\mu\text{mol/L}$ <sup>23</sup>	41% block at 3 $\mu\text{mol/L}$ <sup>23</sup>	Dronedarone 10 times more potent
$I_{Ca-L}$	Guinea pig ventricular myocytes	$IC_{50}=0.18 \mu\text{mol/L}$ <sup>24</sup>		Use- and frequency-dependent blockade
	Canine ventricular myocytes	76% block at 10 $\mu\text{mol/L}$ <sup>25</sup>		
	Rabbit atrioventricular node		85% block at 10 $\mu\text{mol/L}$ <sup>26</sup>	
$I_{Kr}$	Guinea pig ventricular myocytes	$IC_{50} \leq 3 \mu\text{mol/L}$ <sup>24</sup>	$IC_{50}=10 \mu\text{mol/L}$ <sup>29</sup>	Voltage-independent blockade
	Canine ventricular myocytes	97% block at 10 $\mu\text{mol/L}$ <sup>25</sup>		
	Xenopus laevis oocyte	$IC_{50}=9.2 \mu\text{mol/L}$ <sup>27</sup>		
	Mammalian cell system	$IC_{50}=59 \text{ nmol/L}$ <sup>28</sup>	$IC_{50}=70 \text{ nmol/L}$ <sup>28</sup>	
$I_{Ks}$	Guinea pig ventricular myocytes	$IC_{50}=10 \mu\text{mol/L}$ <sup>24</sup>	$IC_{50}>30 \mu\text{mol/L}$ <sup>29</sup>	Voltage-dependent and time-, frequency-, and use-independent blockade
	Xenopus laevis oocyte	33% block at 100 $\mu\text{mol/L}$ <sup>27</sup>		
$I_{to}$	Canine ventricular myocytes	No effect at 10 $\mu\text{mol/L}$ <sup>25</sup>		Cloned human KCNQ1/KCNE1
	Post-MI ventricular myocytes	20% increase at 1 $\mu\text{mol/L}$ <sup>30</sup>		
$I_{K1}$	Guinea pig ventricular myocytes	$IC_{50}>30 \mu\text{mol/L}$ <sup>24</sup>	$IC_{50}=30 \mu\text{mol/L}$ <sup>29</sup>	
$I_{K-ACh}$	Guinea pig atrial myocytes	$IC_{50}=10 \text{ nmol/L}$ <sup>31</sup>	$IC_{50}=1 \mu\text{mol/L}$ <sup>31</sup>	Dronedarone 100 times more potent
	Rabbit SA nodal cells	$IC_{50}=63 \text{ nmol/L}$ <sup>32</sup>		
$\beta$ -adrenergic receptors	Rat heart	$IC_{50}=1.8 \mu\text{mol/L}$ <sup>33</sup>	$IC_{50}=8.7 \mu\text{mol/L}$ <sup>33</sup>	Dose-dependent and noncompetitive inhibition. Agonist-induced increase in adenylate cyclase was also inhibited

$IC_{50}$  indicates concentration that inhibits 50% of current;  $I_{Ca-L}$ , L type calcium current;  $I_{K-ACh}$ , acetylcholine activated potassium current;  $I_{K1}$ , inwardly rectified potassium current;  $I_{Ks}$ , slowly activating delayed rectifier potassium current;  $I_{Kr}$ , rapidly activating delayed rectifier potassium current;  $I_{Na}$ , peak inward sodium current; and SA, sinoatrial.

substrate, leads to a 2- to 4-fold increase in simvastatin levels and the potential for statin-induced myopathy.<sup>41</sup>

Dronedarone is also a CYP2D6 inhibitor and causes a modest increase in bioavailability of metoprolol in CYP2D6 extensive metabolizers.<sup>47</sup> Dronedarone, like amiodarone, causes partial inhibition of tubular transport of creatinine, which leads to increases in serum creatinine concentration that is not related to reduced glomerular filtration.<sup>48</sup>

There are limited data available on dose response and dose titration. On the basis of its pivotal clinical trials, dronedarone can only be dosed at 400 mg twice daily. Adjustments in the amount prescribed predicated on age, gender, race, renal function, tolerance, or the use of concomitant interacting drugs have not been studied and therefore cannot be recommended.

### Clinical Trials

A brief summary of clinical trials is provided in Table 2. Clinical trials are categorized by their primary intention: studies of rhythm control, rate control, mortality/morbidity, or comparative efficacy.

#### Rhythm Control

The Dronedarone Atrial Fibrillation Study after Electrical Cardioversion (DAFNE) was a double-blind, randomized, placebo-controlled, dose-finding trial.<sup>49</sup> A total of 270 patients with persistent AF were randomized to receive 800, 1200, or 1600 mg of dronedarone daily versus placebo and

were then followed for 6 months. There was a dose-dependent conversion to sinus rhythm in 5.8%, 8.2%, and 14.8% of patients in the 3 dose groups, respectively, compared with 3.1% in the placebo group. Dronedarone delayed the time to first AF recurrence, but only at the lowest dose of 800 mg (Figure 2). At 6 months, 35% of patients treated with 800 mg of dronedarone were in sinus rhythm compared with 10% in the placebo group. In contrast to this reverse dose effect on rhythm control, dronedarone reduced the ventricular rate during AF better when used at high compared with low doses.

In DAFNE, dronedarone was not associated with thyroid, pulmonary, neurological, ocular, or pulmonary toxicity. Dronedarone treatment led to dose-dependent prolongation of QT interval, but no torsades de pointes cases were reported. Dronedarone-treated patients, especially those treated with the highest doses, had more gastrointestinal toxicity leading to drug discontinuation.

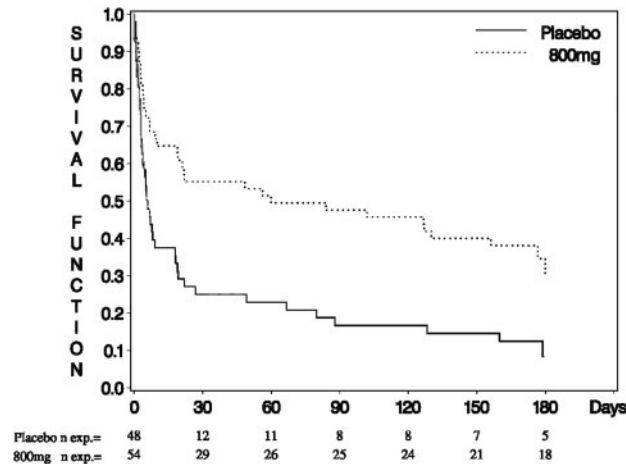
The 400 mg twice daily dose of dronedarone was tested in twin phase 3 studies called The European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS) and the American-Australian-African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS).<sup>50</sup> The EURIDIS and ADONIS trials randomized 1237 patients in sinus rhythm, in a 2:1 ratio of active drug to placebo. The mean age of the study population was 63 years. Although the majority had structural heart disease, the mean

**Table 2. Summary of Clinical Trials Investigating Therapeutic Effects of Dronedarone**

Study	Inclusion Criteria	Specific Exclusion Criteria	Treatment Follow-Up	Results	
				Primary End Points	Secondary End Points
DAFNE <sup>49</sup>	Persistent AF	Permanent AF Atrial flutter NYHA class III or IV CHF LVEF <35%	Placebo vs dronedarone 800, 1200, 1600 mg for 6 months	For 800 mg dose Time to AF recurrence: D: 60 days, P: 5.3 days* SR at end of 6 months: D: 35% P: 10%	Spontaneous conversion to SR: D: 5.8% P: 3.1%* VR during AF recurrence: Reduced by 13.2 bpm
EURIDIS and ADONIS <sup>50</sup>	Paroxysmal AF	Permanent AF NYHA class III/IV CHF Renal insufficiency	Placebo vs dronedarone 400 mg twice daily for 12 months	Time to AF recurrence: D: 116 days P: 53 days* Recurrence rate of AF: D: 64.1% P: 75.2%*	VR during AF recurrence: D: 103.4 ± 25.9 P: 117.1 ± 30.4* Symptomatic AF recurrence: D: 37.7% P: 46%* Hospitalization or death: D: 22.8% P: 30.9%*
ERATO <sup>51</sup>	Permanent AF	NYHA class III/IV CHF	Placebo vs dronedarone 400 mg twice daily for 6 months	Mean VR on 14 <sup>th</sup> day: Reduced by 11.7 bpm*	Change in Mean VR on 14 <sup>th</sup> day during exercise: Reduced by 24.5 bpm* Change in mean resting VR at 4 months: Reduced by 8.8 bpm*
ANDROMEDA <sup>52</sup>	NYHA class III/IV CHF or PND plus LVEF <35%	Recent acute MI Acute pulmonary Edema	Placebo vs dronedarone 400 mg twice daily for 12 months	Death from any cause or hospitalization from worsening heart failure: D: 17.1% P: 12.6% HR=1.38	Death from all cause: D: 8.1% P: 3.8%* (HR=2.13*) Cardiovascular hospitalization: D: 22.9% P: 15.7%*
ATHENA <sup>53-55</sup>	Paroxysmal/persistent AF/atrial flutter plus age ≥75 or age ≥70 + ≥1 risk factor (HTN, DM, stroke, TIA, LA ≥50 mm or LVEF ≤40%)	Permanent AF Unstable hemodynamic situation NYHA class IV CHF	Placebo vs dronedarone 400 mg twice daily for 12 months	Death from all causes or first occurrence of cardiovascular hospitalization: 24.2% RR reduction* HR: 0.76*	Death from any cause: 16% fewer deaths with dronedarone Cardiovascular deaths: 29% RR reduction* Cardiovascular hospitalization: 26% RR reduction* Incidence of stroke: 34% RR reduction* Length of hospitalization: Reduced by 1.26 day/patient/year*
DIONYSOS <sup>56</sup>	Persistent AF	Not reported yet	Dronedarone 400 mg twice daily vs amiodarone 600 mg/day for 28 days followed by 200 mg daily for 6 months	AF recurrence or premature drug discontinuation for intolerance or lack of efficacy: D: 73.9% Amiodarone: 55.3%*	MSE: 20% decrease favoring dronedarone MSE excluding gastrointestinal side effects: 39% decrease favoring dronedarone*

D indicates dronedarone; P, placebo; AF, atrial fibrillation; bpm, beats per minute; CV, cardiovascular; CHF, congestive heart failure; DM, diabetes mellitus; HTN, hypertension; HR, hazard ratio; LA, left atrium; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MSE, Main Safety End points; NYHA, New York heart association; PND, paroxysmal nocturnal dyspnea; RR, relative risk; SR, sinus rhythm; TIA, transient ischemic attack; and VR, ventricular rate.

\*Statistically significant *P* value.



**Figure 2.** Dronedaron increases the time to first recurrence of atrial fibrillation. Kaplan–Meier analysis of the time to first AF recurrence to assigned treatment. The median time to first AF recurrence was significantly delayed to 60 days in patients receiving 800 mg of dronedaron as compared with patients receiving placebo (5.3 days), with relative risk reduction of 55% ( $P=0.001$ ). Data from DAFNE trial. Reproduced from Touboul et al<sup>49</sup> with permission of the publisher. Copyright © 2003, Oxford University Press.

left ventricular ejection fraction was 58%, and only 17% of patients had a history of class I or II congestive heart failure. Ventricular rate and rhythm were monitored by a 12-lead ECG at each scheduled follow-up visit and using transtelephonic electrocardiographic monitoring.

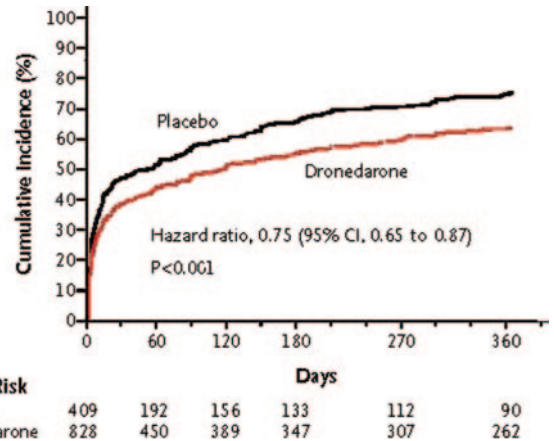
In a prespecified pooled analysis, the median time to first recurrence of AF was 116 days in the dronedaron arm versus 53 days in the placebo group (Figure 3). Dronedaron reduced the ventricular rate during AF recurrence. A post hoc analysis revealed a 27% reduction of relative risk of hospitalization and death with dronedaron treatment. The rates of cardiac and extracardiac adverse events in these trials were comparable to those of the placebo. There was a reported incidence of serum creatinine elevation in 2.4% of the patients in dronedaron group.

Additionally, a small study in patients with implantable cardiac defibrillators found that dronedaron at doses of up to 2000 mg daily had no significant effect on defibrillation and pacing thresholds. There was a trend toward a reduction in appropriate implantable cardiac defibrillators shocks at the highest doses, which were poorly tolerated.<sup>57</sup>

### Rate Control

Efficacy and Safety of Dronedaron for Control of Ventricular Rate (ERATO)<sup>51</sup> was a study of the efficacy of dronedaron for rate control in patients with permanent AF. ERATO investigators randomized 174 elderly patients to 800 mg of dronedaron daily or placebo. Despite prior rate-control therapy with  $\beta$ -blockers, digitalis, or calcium channel antagonists, all patients at study entry had a resting heart rate of  $\geq 80$  beats per minute. The majority again had structural heart disease, but none had severe heart failure.

In the ERATO trial, the addition of dronedaron to standard rate-control therapy reduced the ventricular rate by 11.7 beats per minute on day 14, and the effect was sustained for



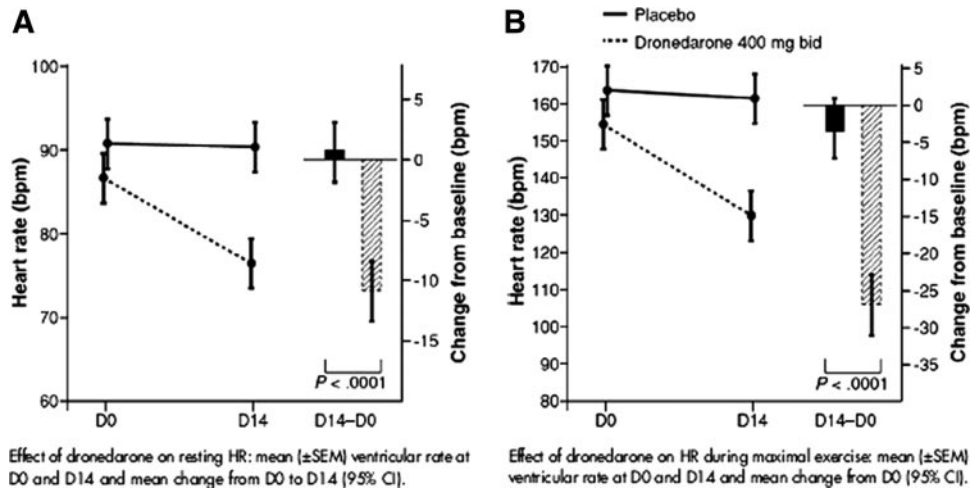
**Figure 3.** Dronedaron reduces the recurrence rate of atrial fibrillation. Kaplan–Meier cumulative incidence curve for the adjudicated first recurrence of atrial fibrillation. At 12 months, the rates of recurrence were 64.1% in the dronedaron group and 75.2% in the placebo group (hazard ratio 0.75; 95% CI, 0.65 to 0.87;  $P<0.001$ ). Combined data from EURIDIS and ADONIS trial. Modified and reproduced from Singh et al<sup>50</sup> with permission of the publisher. Copyright © 2007, the Massachusetts Medical Society.

the 6-month trial period (Figure 4). More pronounced rate control was seen during exercise (mean reduction of 24.5 beats per minute, Figure 4), but this did not translate into improved exercise duration. There were no untoward interactions between dronedaron and other rate control agents or anticoagulants, except for a 41% increase in serum digoxin concentration.<sup>51</sup>

### Mortality and Morbidity

Antiarrhythmic Trial with Dronedaron in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) was a mortality trial in which dronedaron was compared with placebo in patients with moderate to severe heart failure, regardless of their arrhythmia history.<sup>52</sup> One thousand hospitalized patients with New York Heart Association class III or IV congestive heart failure and left ventricular ejection fraction  $<35\%$  were to receive 800 mg of dronedaron daily or placebo. After 627 patients were enrolled, the trial was prematurely terminated. During a median follow-up of 2 months, a significantly higher mortality rate was reported with dronedaron treatment (8.1%) as compared with placebo (3.8%), primarily due to worsening congestive heart failure. The risk of death and hospitalization was higher in patients with the most severe left ventricular systolic dysfunction. A retrospective analysis identified a higher death rate in patients who were withdrawn from angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, but how much this contributed to the death imbalance is uncertain. Potent inhibition of peak sodium current and resultant impairment of ventricular contractility may be another possible explanation for worsening heart failure.<sup>23</sup>

Assess the Efficacy of Dronedaron for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter (ATHENA) enrolled patients with stable AF who had at least 1 cardio-

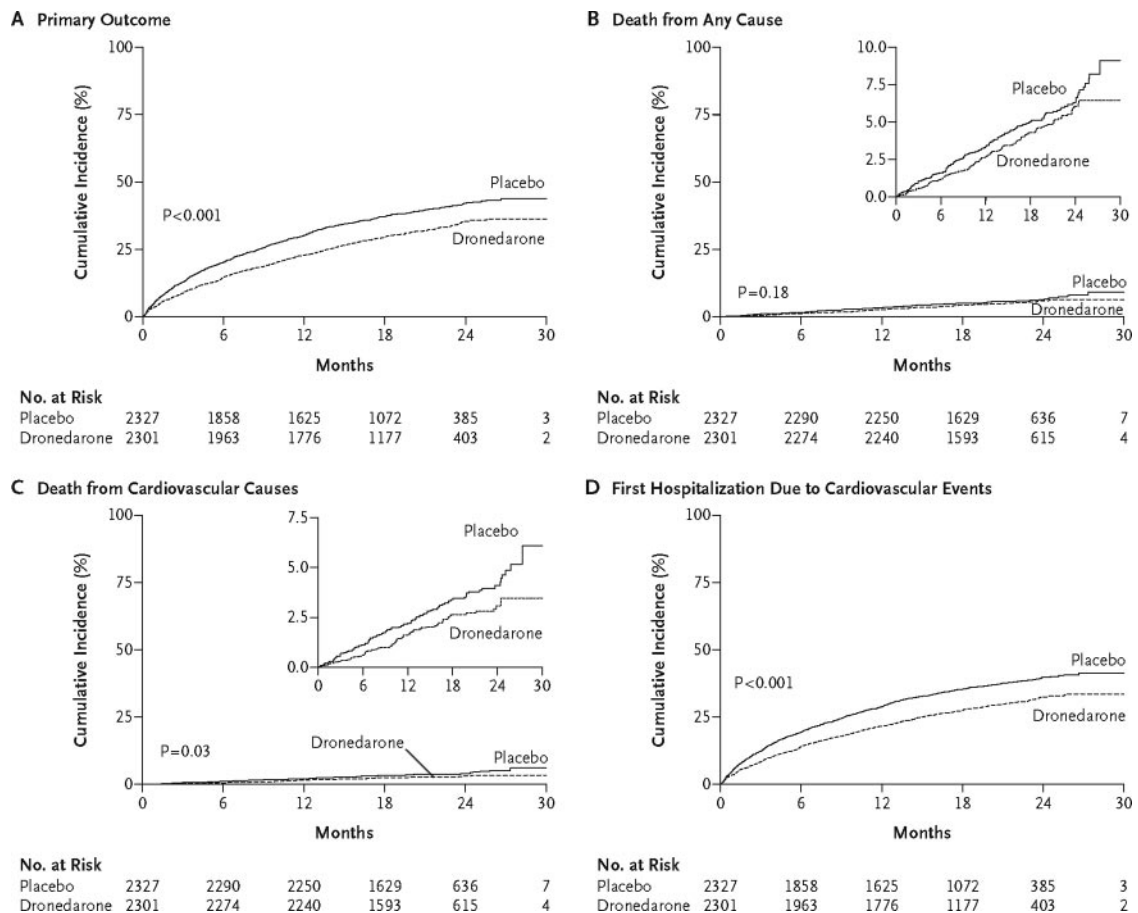


**Figure 4.** Dronedaron reduces the mean ventricular rate during rest (A) and exercise (B) in atrial fibrillation. Treatment with dronedaron reduced the mean 24-hour ventricular rate by 11.7 beats/min during rest and by 24.5 beats/min during exercise on day 14. Data from ERATO trial. Modified and reproduced from Davy et al,<sup>51</sup> copyright © 2008, with permission from Elsevier.

vascular risk factor.<sup>54</sup> Unlike prior studies, this trial had a composite primary end point of all-cause mortality and cardiovascular hospitalization. ATHENA investigators randomized 4628 patients with a history of paroxysmal or

persistent AF/atrial flutter to dronedaron 400 mg twice a day versus placebo with 12 months of follow-up.

The results of the ATHENA trial are shown in Figure 5.<sup>54</sup> Treatment with dronedaron was associated with highly



**Figure 5.** Kaplan–Meier cumulative incidences of the primary and secondary outcomes in the ATHENA trial. Treatment with dronedaron significantly reduced the occurrence of (A) the composite primary outcome of first hospitalization due to cardiovascular events or death from any cause (hazard ratio [HR] 0.76), (C) secondary outcomes of death from cardiovascular causes (HR 0.71), and (D) first hospitalization due to cardiovascular events (HR 0.74). (B) There was no difference in all-cause mortality (HR 0.84). Reproduced from Hohnloser et al<sup>54</sup> with permission from the publisher. Copyright © 2009, the Massachusetts Medical Society.

**Table 3. Selected Adverse Events and Laboratory Abnormalities in Patients Receiving Dronedaronone in the ATHENA Trial**

Event	Dronedaronone (n = 2291)	Placebo (n = 2313)	P Value
Any TEAE	72.0	69.3	0.048
Bradycardia	3.5	1.2	<0.001
QT-interval prolongation	1.7	0.6	<0.001
Interstitial lung disease	0.2	0.2	1.0
Diarrhea	9.7	6.2	<0.001
Nausea	5.3	3.1	<0.001
Abnormal liver function test	0.5	0.6	0.84
Hypothyroidism	0.5	0.3	0.23
Hyperthyroidism	0.3	0.3	1.00
Rash	3.4	2.0	0.006
Serum creatinine increase	4.7	1.3	<0.001
Any serious TEAE	19.9	21.1	0.31
Premature discontinuation of study drug because of an adverse event	12.7	8.1	<0.001

TEAEs indicates treatment-emergent adverse events.

Data borrowed from Hohnloser et al.<sup>54</sup>

statistically significant reductions in the primary end point and several of the secondary end points. There was a trend toward lower overall mortality with dronedaronone treatment, and, importantly, there was a statistically significant reduction in death due to cardiac arrhythmias (hazard ratio 0.55;  $P=0.01$ ). Because dronedaronone blocks sodium current as well as multiple potassium currents, it increases the ventricular effective refractory period, which may account for ventricular arrhythmia suppression.<sup>43,44</sup> The most frequently reported adverse effect of dronedaronone was gastrointestinal, principally nausea and diarrhea that in several cases led to drug discontinuation (Table 3). The reduction in cardiovascular hospitalizations was accounted for mostly by fewer admissions for AF. A post hoc analysis demonstrated that dronedaronone was associated with a significant reduction in the adjusted risk of stroke compared with placebo, a benefit that was preserved in patients who were already receiving anti-thrombotic therapy.<sup>53</sup>

### Comparative Efficacy

A clinical trial directly comparing dronedaronone with amiodarone for maintenance of sinus rhythm in AF called Efficacy and Safety of Dronedaronone versus Amiodarone for the maintenance of Sinus Rhythm in Patients with AF (DIONYSOS) recently concluded. The results have not been presented in full.<sup>56</sup> DIONYSOS randomized 504 patients with persistent AF to dronedaronone (400 mg BID) versus amiodarone (600 mg daily for 28 days and then 200 mg daily) for a minimum of 6 months. The primary end point was a composite of ECG-documented AF recurrence or premature study drug discontinuation for intolerance or lack of efficacy. At a mean follow-up of 7 months, fewer amiodarone-treated patients reached the primary end point compared with those treated with dronedaronone (55.3% versus 73.9%,  $P<0.001$ ), indicat-

ing that amiodarone showed better sustained efficacy than dronedaronone. More gastrointestinal adverse events (diarrhea, vomiting, and nausea) and fewer cardiac adverse events (bradycardia, QT prolongation) were noted in the dronedaronone arm.

### Conclusions

Like amiodarone, dronedaronone has effects on multiple cardiac ion channels and receptors. In several clinical trials, dronedaronone has been proven to maintain sinus rhythm and to control the ventricular rate during episodes of AF. In ATHENA, dronedaronone reduced cardiovascular hospitalizations and mortality in high-risk patients with AF.<sup>53,55</sup> Dronedaronone has a well-described side effect profile; the principle adverse effect is diarrhea, which may necessitate drug discontinuation. Dronedaronone causes dose-dependent prolongation of QTc interval, but torsades de pointes is rare.<sup>49,50,54</sup> The drug increases serum creatinine by inhibition of tubular secretion. This effect is not associated with reduced renal function and is reversible, but needs to be considered, particularly in patients receiving other drugs like angiotensin-converting enzyme inhibitors that also increase serum creatinine.<sup>48</sup>

The safety of dronedaronone in patients with advanced heart failure is a concern.<sup>52</sup> Although ATHENA included patients with heart failure, it excluded severely ill patients with advanced heart failure and hemodynamic instability. Only 4.4% subjects in ATHENA had New York Heart Association class III heart failure, and only 3.9% patients had left ventricular ejection fraction <35%. Therefore, the results of the ATHENA trial do not directly counter the concerns raised by the ANDROMEDA trial. Until more data are available, patients with severe systolic heart failure and hemodynamic instability should not receive dronedaronone.

As of this writing, dronedaronone is under review by regulatory agencies. It is likely to be available for patients with AF with severe associated symptoms, in particular those with risk factors for stroke and heart failure. Although not a panacea, it will provide another useful option for patients afflicted with this common and troubling disease.

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