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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.[1,2] It is an epidemic. It is projected that by 2050, more than 15 million people will contract AF in the United States alone.[2,3] Nearly 1 in every 10 persons aged 80 years and older has AF,[1,4,5] predisposing them to stroke, heart failure, and death.[6,7] A recent report from *Centers for Medicare and Medicaid Services* suggested that AF accounted for 1 765 304 hospitalizations in 1999.[8] The cost of medical care for patients with AF is almost 5 times higher than the care of patients without AF.[9,10] 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.[2,11]

Current therapy for AF is multidimensional and complicated.[12] 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,[13–18] 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.[19–21] 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.[23–33] In patch clamp experiments using human atrial myocytes, 3 μmol/L of dronedarone produced potent blockade of peak sodium current, an effect 10-fold greater than that of an equal concentration of amiodarone.[23] 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.[24] Additionally, dronedarone exhibited strong inhibitory effects on the acetylcholine-activated potassium current ($I_{K\text{-}Ach}$) in rabbit sinoatrial nodal cells[32] and guinea pig atrial cells.[31] Blockade of $I_{K\text{-}Ach}$ by dronedarone was 100 times more potent than that of amiodarone.[31] 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.[34,35]

Like amiodarone, dronedarone exerts its antiadrenergic effects by noncompetitive binding to β-adrenergic receptors and inhibition of agonist-induced increases in adenylate cyclase activity.[33] Dronedarone (0.01 to 1 μmol/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.[36]

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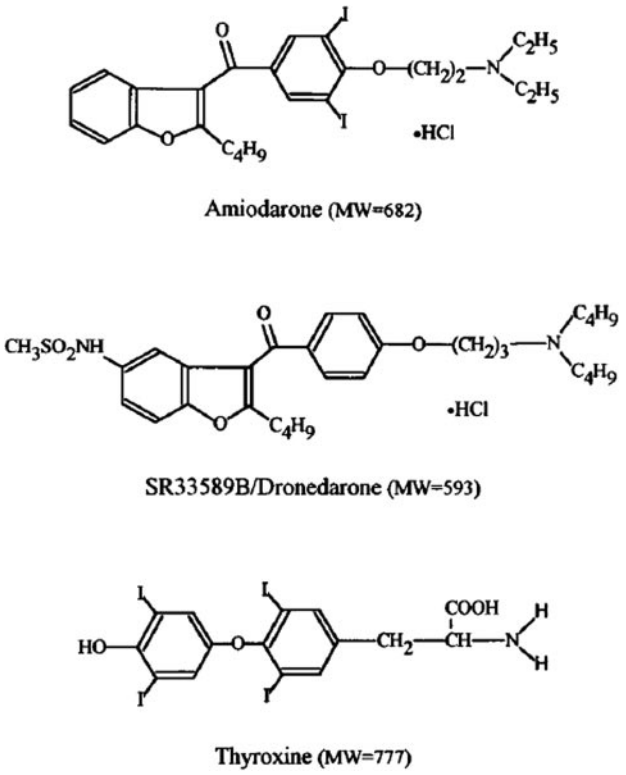

Figure 1. Molecular structure of amiodarone, dronedarone, and thyroxine. As compared with amiodarone, in the dronedarone molecule, ethyl groups on the terminal nitrogen are replaced by butyls groups, the iodine moiety is removed, and a methanesulfonyl group has been added to benzofuran ring. Reproduced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

The effect of dronedarone 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 μmol/L of dronedarone decreased action potential duration in rabbit papillary muscle,[22] rabbit atrial muscle,[37] and the canine papillary muscle preparation,[25] with no effect on guinea pig ventricular myocytes.[24] On the other hand, sustained administration of drug increased action potential duration in rabbit papillary muscles[22] and rabbit atrial muscles.[37] The action potential duration of dog papillary muscle remained unchanged.[25] In canine left ventricular Purkinje fibers, 10 μmol/L of dronedarone reduced the incidence of early and delayed afterdepolarizations evoked by dofetilide and ouabain, respectively.[25] Similarly, dronedarone reduced transmural dispersion of repolarization and abolished d-sotalol–induced early afterdepolarizations in canine left ventricular tissue slices.[38]

Thus dronedarone 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 dronedarone on ventricular repolarization depend on duration of drug administration and species. Although acute administration of dronedarone abbreviates repolarization,[39] sustained administration increases the QTc interval.[40] The difference in electrophysiological effects between acute versus sustained administration may be partially due to the fact that dronedarone and amiodarone are highly protein-bound in vivo.[41,42] Therefore, it is difficult to directly extrapolate in vitro effects of dronedarone to its in vivo actions.

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

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

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

Pharmacokinetics

Dronedarone is well absorbed (≈70% to 94%) after oral administration, and absorption increases 2- to 3-fold when it is taken with food. Dronedarone 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.[41] The clearance of dronedarone is principally nonrenal, with a terminal half-life of ≈24 hours.

Dronedarone is a substrate for and a moderate inhibitor of CYP3A4.[41] A potent CYP3A4 inhibitor such as ketoconazole may increase dronedarone exposure by as much as 25-fold. Consequently, dronedarone 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.[41]

Concomitant administration of dronedarone 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.[41] This necessitates frequent monitoring of digoxin concentration and possible dose reduction. Coadministration of dronedarone 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 μmol/L[23]	41% block at 3 μmol/L[23]	Dronedarone 10 times more potent
$I_{Ca\text{-}L}$	Guinea pig ventricular myocytes	IC_{50}=0.18 μmol/L[24]		Use- and frequency-dependent blockade
	Canine ventricular myocytes	76% block at 10 μmol/L[25]		
	Rabbit atrioventricular node		85% block at 10 μmol/L[26]	
I_{Kr}	Guinea pig ventricular myocytes	$IC_{50} \leq 3$ μmol/L[24]	IC_{50}=10 μmol/L[29]	Voltage-independent blockade
	Canine ventricular myocytes	97% block at 10 μmol/L[25]		
	Xenopus laevis oocyte	IC_{50}=9.2 μmol/L[27]		
	Mammalian cell system	IC_{50}=59 nmol/L[28]	IC_{50}=70 nmol/L[28]	Voltage-dependent, use-independent blockade
I_{Ks}	Guinea pig ventricular myocytes	IC_{50}=10 μmol/L[24]	$IC_{50}>30$ μmol/L[29]	Voltage-dependent and time-, frequency-, and use-independent blockade
	Xenopus laevis oocyte	33% block at 100 μmol/L[27]		Cloned human KCNQ1/KCNE1
I_{to}	Canine ventricular myocytes	No effect at 10 μmol/L[25]		
	Post-MI ventricular myocytes	20% increase at 1 μmol/L[30]		
I_{K1}	Guinea pig ventricular myocytes	$IC_{50}>30$ μmol/L[24]	IC_{50}=30 μmol/L[29]	
$I_{K\text{-}ACh}$	Guinea pig atrial myocytes	IC_{50}=10 nmol/L[31]	IC_{50}=1 μmol/L[31]	Dronedarone 100 times more potent
	Rabbit SA nodal cells	IC_{50}=63 nmol/L[32]		
β-adrenergic receptors	Rat heart	IC_{50}= 1.8 μmol/L[33]	IC_{50}=8.7 μmol/L[33]	Dose-dependent and noncompetitive inhibition. Agonist-induced increase in adenylate cyclase was also inhibited

IC_{50} indicates concentration that inhibits 50% of current; $I_{Ca\text{-}L}$, L type calcium current; $I_{K\text{-}Ach}$, 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.[41]

Dronedarone is also a CYP2D6 inhibitor and causes a modest increase in bioavailability of metoprolol in CYP2D6 extensive metabolizers.[47] 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.[48]

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.[49] 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).[50] 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[49]	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 bmp
EURIDIS and ADONIS[50]	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[51]	Permanent AF	NYHA class III/IV CHF	Placebo vs dronedarone 400 mg twice daily for 6 months	Mean VR on 14th day: Reduced by 11.7 bpm*	Change in Mean VR on 14th day during exercise: Reduced by 24.5 bpm* Change in mean resting VR at 4 months: Reduced by 8.8 bpm*
ANDROMEDA[52]	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[53–55]	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[56]	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.

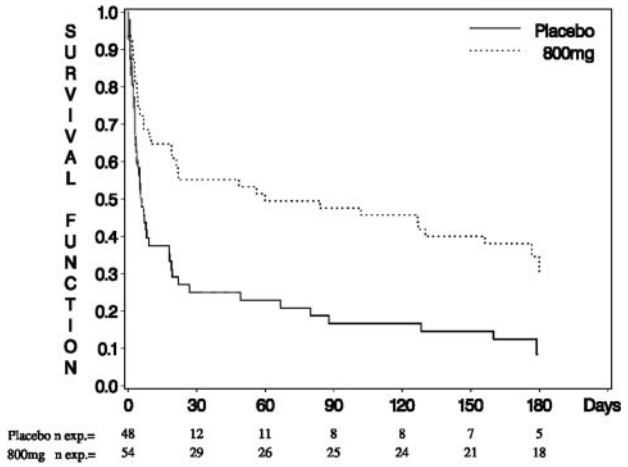

Figure 2. Dronedarone increases the time to first recurrence of atrial fibrillation. Kaplan–Meier analysis of the time to first AF recurrence to assigned treatment. The median time to first AF recurrence was significantly delayed to 60 days in patients receiving 800 mg of dronedarone as compared with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

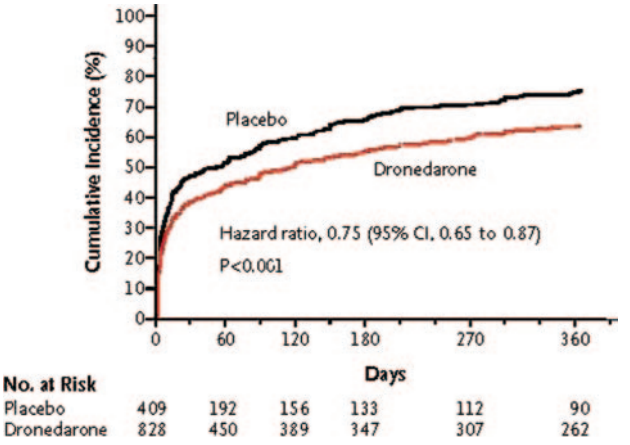

Figure 3. Dronedarone reduces the recurrence rate of atrial fibrillation. Kaplan–Meier cumulative incidence curve for the adjudicated first recurrence of atrial fibrillation. At 12 months, the rates of recurrence were 64.1% in the dronedarone group and 75.2% in the placebo group (hazard ratio 0.75; 95%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

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 dronedarone arm versus 53 days in the placebo group (Figure 3). Dronedarone reduced the ventricular rate during AF recurrence. A post hoc analysis revealed a 27% reduction of relative risk of hospitalization and death with dronedarone 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 dronedarone group.

Additionally, a small study in patients with implantable cardiac defibrillators found that dronedarone 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.[57]

Rate Control

Efficacy and Safety of Dronedarone for Control of Ventricular Rate (ERATO)[51] was a study of the efficacy of dronedarone for rate control in patients with permanent AF. ERATO investigators randomized 174 elderly patients to 800 mg of dronedarone daily or placebo. Despite prior rate-control therapy with β-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 dronedarone to standard rate-control therapy reduced the ventricular rate by 11.7 beats per minute on day 14, and the effect was sustained for 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 dronedarone and other rate control agents or anticoagulants, except for a 41% increase in serum digoxin concentration.[51]

Mortality and Morbidity

Antiarrhythmic Trial with Dronedarone in Moderate-to-Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA) was a mortality trial in which dronedarone was compared with placebo in patients with moderate to severe heart failure, regardless of their arrhythmia history.[52] 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 dronedarone 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 dronedarone 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.[23]

Assess the Efficacy of Dronedarone 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-

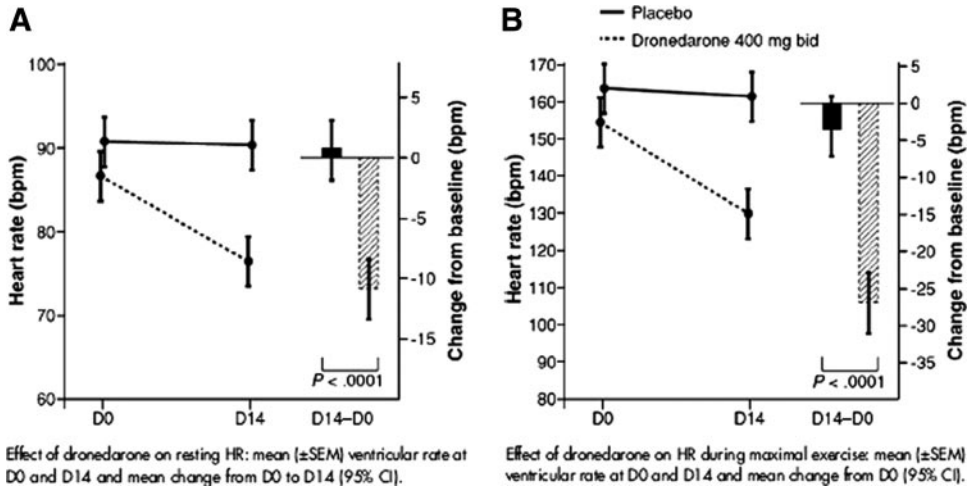

Figure 4. Dronedarone reduces the mean ventricular rate during rest (A) and exercise (B) in atrial fibrillation. Treatment with dronedarone reduced the mean 24-hour ventricular rate by 11.7 beats/min during rest and by 24.5 beats/min during exercise on day 14. Data from ERATO trial. Modified and reproduced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

vascular risk factor.[54] 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 dronedarone 400 mg twice a day versus placebo with 12 months of follow-up.

The results of the ATHENA trial are shown in Figure 5.[54] Treatment with dronedarone was associated with highly

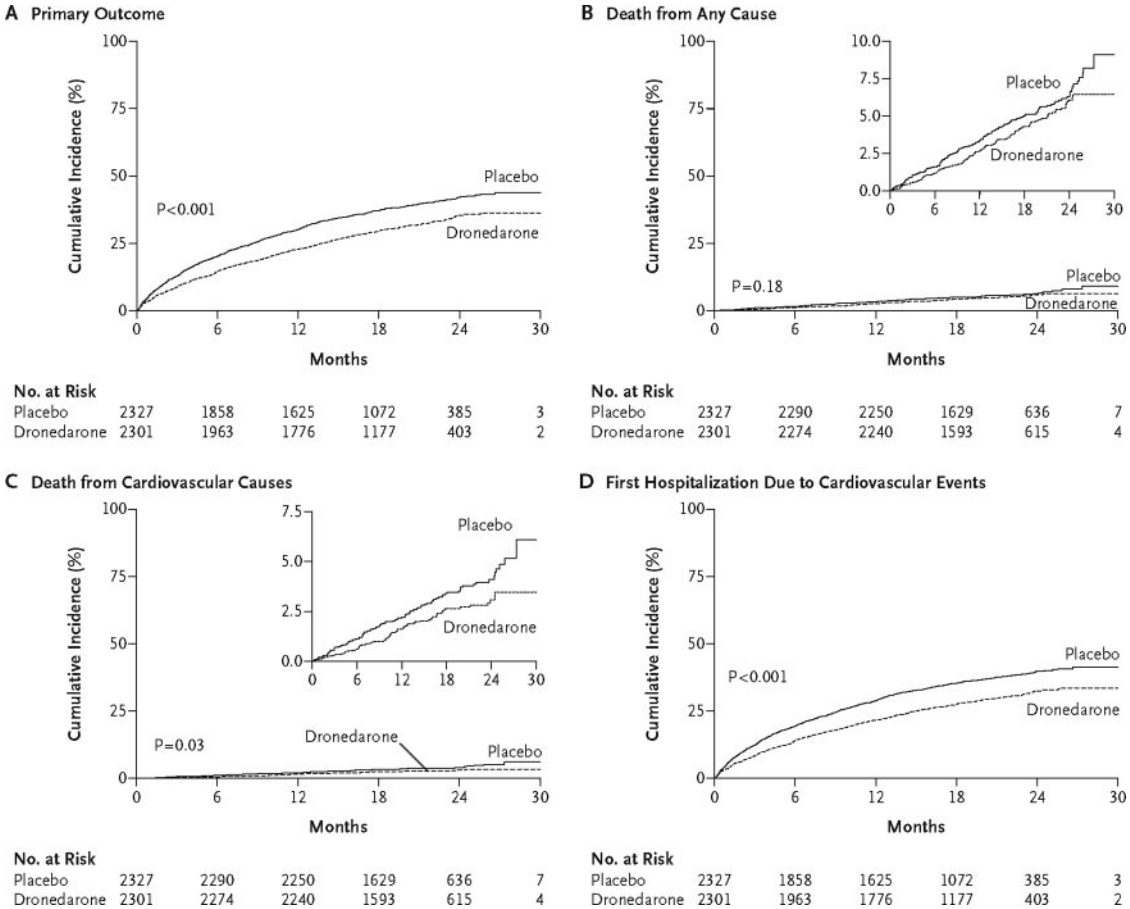

Figure 5. Kaplan–Meier cumulative incidences of the primary and secondary outcomes in the ATHENA trial. Treatment with dronedarone significantly reduced the occurrence of (A) the composite primary outcome of first hospitalization due to cardiovascular events or death from any cause (hazard ratio [HR] 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[54] with permission from the publisher. Copyright © 2009, the Massachusetts Medical Society.

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

Event	Dronedarone (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.[54]

statistically significant reductions in the primary end point and several of the secondary end points. There was a trend toward lower overall mortality with dronedarone treatment, and, importantly, there was a statistically significant reduction in death due to cardiac arrhythmias (hazard ratio 0.55; $P=0.01$). Because dronedarone blocks sodium current as well as multiple potassium currents, it increases the ventricular effective refractory period, which may account for ventricular arrhythmia suppression.[43,44] The most frequently reported adverse effect of dronedarone 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 dronedarone 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 antithrombotic therapy.[53]

Comparative Efficacy

A clinical trial directly comparing dronedarone with amiodarone for maintenance of sinus rhythm in AF called Efficacy and Safety of Dronedarone versus Amiodarone for the maintenance of Sinus Rhythm in Patients with AF (DIONYSOS) recently concluded. The results have not been presented in full.[56] DIONYSOS randomized 504 patients with persistent AF to dronedarone (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 dronedarone (55.3% versus 73.9%, $P<0.001$), indicating that amiodarone showed better sustained efficacy than dronedarone. More gastrointestinal adverse events (diarrhea, vomiting, and nausea) and fewer cardiac adverse events (bradycardia, QT prolongation) were noted in the dronedarone arm.

Conclusions

Like amiodarone, dronedarone has effects on multiple cardiac ion channels and receptors. In several clinical trials, dronedarone has been proven to maintain sinus rhythm and to control the ventricular rate during episodes of AF. In ATHENA, dronedarone reduced cardiovascular hospitalizations and mortality in high-risk patients with AF.[53,55] Dronedarone has a well-described side effect profile; the principle adverse effect is diarrhea, which may necessitate drug discontinuation. Dronedarone causes dose-dependent prolongation of QTc interval, but torsades de pointes is rare.[49,50,54] 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.[48]

The safety of dronedarone in patients with advanced heart failure is a concern.[52] 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 dronedarone.

As of this writing, dronedarone 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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Dr. Kowey has been an ad hoc consultant to Wyeth and to Sanofi-Aventis during the preclinical and clinical development of amiodarone and dronedarone. He has not enrolled patients into clinical trials of dronedarone and holds no equity interest in these or any other pharmaceutical firms.

References

1. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. *Arch Intern Med.* 1995;155:469–473.
2. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA.* 2001;285:2370–2375.

3. Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation*. 2006;114:119–125.
4. Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol*. 1994;74:236–241.
5. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, White R, Furberg CD, Rautaharju PM. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997;96:2455–2461.
6. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. *Am J Med*. 2002;113:359–364.
7. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med*. 1987; 147:1561–1564.
8. Public health and aging: atrial fibrillation as a contributing cause of death and medicare hospitalization: United states, 1999. *MMWR Morb Mortal Wkly Rep*. 2003;52:128–131.
9. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. *Arch Intern Med*. 1998;158:229–234.
10. Wu EQ, Birnbaum HG, Mareva M, Tuttle E, Castor AR, Jackman W, Ruskin J. Economic burden and co-morbidities of atrial fibrillation in a privately insured population. *Curr Med Res Opin*. 2005;21:1693–1699.
11. Wattigney WA, Mensah GA, Croft JB. Increased atrial fibrillation mortality: United States, 1980–1998. *Am J Epidemiol*. 2002;155:819–826.
12. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Le Heuzey JY, Kay GN, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann S, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Halperin JL, Hunt SA, Nishimura R, Ornato JP, Page RL, Riegel B, Priori SG, Blanc JJ, Budaj A, Camm AJ, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114: e257–e354.
13. Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, Bourassa MG, Arnold JM, Buxton AE, Camm AJ, Connolly SJ, Dubuc M, Ducharme A, Guerra PG, Hohnloser SH, Lambert J, Le Heuzey JY, O'Hara G, Pedersen OD, Rouleau JL, Singh BN, Stevenson LW, Stevenson WG, Thibault B, Waldo AL. Rhythm control versus rate control for atrial fibrillation and heart failure. *N Engl J Med*. 2008;358:2667–2677.
14. Carlsson J, Miketic S, Windeler J, Cuneo A, Haun S, Micus S, Walter S, Tebbe U. Randomized trial of rate-control versus rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol*. 2003;41:1690–1696.
15. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation: Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *Lancet*. 2000;356:1789–1794.
16. Opolski G, Torbicki A, Kosior DA, Szulc M, Wozakowska-Kaplon B, Kolodziej P, Achremczyk P. Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study. *Chest*. 2004;126:476–486.
17. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA, Darmanata JI, Timmermans AJ, Tijssen JG, Crijns HJ. Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group: A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347: 1834–1840.
18. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD. Atril Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) investigators: a comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825–1833.
19. Corley SD, Epstein AE, DiMarco JP, Domanski MJ, Geller N, Greene HL, Josephson RA, Kellen JC, Klein RC, Krahn AD, Mickel M, Mitchell LB, Nelson JD, Rosenberg Y, Schron E, Shemanski L, Waldo AL, Wyse DG. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. *Circulation*. 2004;109:1509–1513.
20. Steinberg JS, Sadaniantz A, Kron J, Krahn A, Denny DM, Daubert J, Campbell WB, Havranek E, Murray K, Olshansky B, O'Neill G, Sami M, Schmidt S, Storm R, Zabalgoitia M, Miller J, Chandler M, Nasco EM, Greene HL. Analysis of cause-specific mortality in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. *Circulation*. 2004;109:1973–1980.
21. Zimetbaum P. Is rate control or rhythm control preferable in patients with atrial fibrillation? An argument for maintenance of sinus rhythm in patients with atrial fibrillation. *Circulation*. 2005;111:3150–3156.
22. Sun W, Sarma JS, Singh BN. Electrophysiological effects of dronedarone (SR33589), a noniodinated benzofuran derivative, in the rabbit heart: comparison with amiodarone. *Circulation*. 1999;100:2276–2281.
23. Lalevee N, Nargeot J, Barrere-Lemaire S, Gautier P, Richard S. Effects of amiodarone and dronedarone on voltage-dependent sodium current in human cardiomyocytes. *J Cardiovasc Electrophysiol*. 2003; 14:885–890.
24. Gautier P, Guillemare E, Marion A, Bertrand JP, Tourneur Y, Nisato D. Electrophysiologic characterization of dronedarone in guinea pig ventricular cells. *J Cardiovasc Pharmacol*. 2003;41:191–202.
25. Varro A, Takacs J, Nemeth M, Hala O, Virag L, Iost N, Balati B, Agoston M, Vereckei A, Pastor G, Delbruyere M, Gautier P, Nisato D, Papp JG. Electrophysiological effects of dronedarone (SR 33589), a noniodinated amiodarone derivative in the canine heart: comparison with amiodarone. *Br J Pharmacol*. 2001;133:625–634.
26. Hancox JC. Amiodarone blocks L-type calcium current in single myocytes isolated from the rabbit atrioventricular node. *Gen Pharmacol*. 1997;29:429–435.
27. Thomas D, Kathofer S, Zhang W, Wu K, Wimmer AB, Zitron E, Kreye VA, Katus HA, Schoels W, Karle CA, Kiehn J. Acute effects of dronedarone on both components of the cardiac delayed rectifier K+ current, HERG and KvLQT1/minK potassium channels. *Br J Pharmacol*. 2003; 140:996–1002.
28. Ridley JM, Milnes JT, Witchel HJ, Hancox JC. High affinity HERG K(+) channel blockade by the antiarrhythmic agent dronedarone: resistance to mutations of the S6 residues Y652 and F656. *Biochem Biophys Res Commun*. 2004;325:883–891.
29. Guillemare E, Marion A, Nisato D, Gautier P. Acute effects of dronedarone and amiodarone on iK1, iKr and iKs in guinea pig ventricular myocytes. *Fund Clin Pharmacol*. 1999;13:289.
30. Aimond F, Beck L, Gautier P, Cherif OK, Davy JM, Lorente P, Nisato D, Vassort G. Cellular and in vivo electrophysiological effects of dronedarone in normal and postmyocardial infarcted rats. *J Pharmacol Exp Ther*. 2000;292:415–424.
31. Guillemare E, Marion A, Nisato D, Gautier P. Inhibitory effects of dronedarone on muscarinic K+ current in guinea pig atrial cells. *J Cardiovasc Pharmacol*. 2000;36:802–805.
32. Altomare C, Barbuti A, Viscomi C, Baruscotti M, DiFrancesco D. Effects of dronedarone on acetylcholine-activated current in rabbit SAN cells. *Br J Pharmacol*. 2000;130:1315–1320.
33. Chatelain P, Meysmans L, Matteazzi JR, Beaufort P, Clinet M. Interaction of the antiarrhythmic agents SR 33589 and amiodarone with the beta-adrenoceptor and adenylate cyclase in rat heart. *Br J Pharmacol*. 1995;116:1949–1956.
34. Cha TJ, Ehrlich JR, Chartier D, Qi XY, Xiao L, Nattel S. Kir3-based inward rectifier potassium current: potential role in atrial tachycardia remodeling effects on atrial repolarization and arrhythmias. *Circulation*. 2006;113:1730–1737.
35. Dobrev D, Friedrich A, Voigt N, Jost N, Wettwer E, Christ T, Knaut M, Ravens U. The G protein-gated potassium current I(K, ACh) is constitutively active in patients with chronic atrial fibrillation. *Circulation*. 2005; 112:3697–3706.
36. Guiraudou P, Pucheu SC, Gayraud R, Gautier P, Roccon A, Herbert JM, Nisato D. Involvement of nitric oxide in amiodarone- and dronedarone-induced coronary vasodilation in guinea pig heart. *Eur J Pharmacol*. 2004;496:119–127.
37. Sun W, Sarma JS, Singh BN. Chronic and acute effects of dronedarone on the action potential of rabbit atrial muscle preparations: comparison with amiodarone. *J Cardiovasc Pharmacol*. 2002;39:677–684.
38. Moro S, Ferreiro M, Celestino D, Medei E, Elizari MV, Sicouri S. In vitro effects of acute amiodarone and dronedarone on epicardial, endocardial, and M cells of the canine ventricle. *J Cardiovasc Pharmacol Ther*. 2007;12:314–321.

39. Verduyn SC, Vos MA, Leunissen HD, van Opstal JM, Wellens HJ. Evaluation of the acute electrophysiologic effects of intravenous dronedarone, an amiodarone-like agent, with special emphasis on ventricular repolarization and acquired torsade de pointes arrhythmias. *J Cardiovasc Pharmacol*. 1999;33:212–222.
40. van Opstal JM, Schoenmakers M, Verduyn SC, de Groot SH, Leunissen JD, van Der Hulst FF, Molenschot MM, Wellens HJ, Vos MA. Chronic amiodarone evokes no torsade de pointes arrhythmias despite QT lengthening in an animal model of acquired long-QT syndrome. *Circulation*. 2001;104: 2722–2727.
41. European Medicines Agency: Withdrawal Public Assessment Report Of the Marketing Authorisation Application for Multaq. Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/multaq/361489en4.pdf. Accessed July 21, 2009.
42. Podrid PJ. Amiodarone: reevaluation of an old drug. *Ann Intern Med*. 1995;122:689–700.
43. Manning AS, Bruyninckx C, Ramboux J, Chatelain P. SR 33589, a new amiodarone-like agent: effect on ischemia- and reperfusion-induced arrhythmias in anesthetized rats. *J Cardiovasc Pharmacol*. 1995;26: 453–461.
44. Finance O, Manning A, Chatelain P. Effects of a new amiodarone-like agent, SR 33589, in comparison to amiodarone, D,L-sotalol, and lignocaine, on ischemia-induced ventricular arrhythmias in anesthetized pigs. *J Cardiovasc Pharmacol*. 1995;26:570–576.
45. Djandjighian L, Planchenault J, Finance O, Pastor G, Gautier P, Nisato D. Hemodynamic and antiadrenergic effects of dronedarone and amiodarone in animals with a healed myocardial infarction. *J Cardiovasc Pharmacol*. 2000;36:376–383.
46. Hodeige D, Heyndrickx JP, Chatelain P, Manning A. SR 33589, a new amiodarone-like antiarrhythmic agent: anti-adrenoceptor activity in anaesthetized and conscious dogs. *Eur J Pharmacol*. 1995;279:25–32.
47. Damy T, Pousset F, Caplain H, Hulot JS, Lechat P. Pharmacokinetic and pharmacodynamic interactions between metoprolol and dronedarone in extensive and poor CYP2D6 metabolizers healthy subjects. *Fundam Clin Pharmacol*. 2004;18:113–123.
48. Tschuppert Y, Buclin T, Rothuizen LE, Decosterd LA, Galleyrand J, Gaud C, Biollaz J. Effect of dronedarone on renal function in healthy subjects. *Br J Clin Pharmacol*. 2007;64:785–791.
49. Touboul P, Brugada J, Capucci A, Crijns HJ, Edvardsson N, Hohnloser SH. Dronedarone for prevention of atrial fibrillation: a dose-ranging study. *Eur Heart J*. 2003;24:1481–1487.
50. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey PR, Capucci A, Radzik D, Aliot EM, Hohnloser SH. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med*. 2007;357:987–999.
51. Davy JM, Herold M, Hoglund C, Timmermans A, Alings A, Radzik D, Van KL. Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the Efficacy and safety of dRonedArone for the cOntrol of ventricular rate during atrial fibrillation (ERATO) study. *Am Heart J*. 2008;156:527–529.
52. Kober L, Torp-Pedersen C, McMurray JJ, Gotzsche O, Levy S, Crijns H, Amlie J, Carlsen J. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med*. 2008;358:2678–2687.
53. Connolly SJ. The effect of dronedarone on cardiovascular outcomes and stroke in patients with atrial fibrillation. European Society of Cardiology Congress, August 30–September 3, 2008, Munich, Germany. Clinical trials update 3, 2008.
54. Hohnloser SH, Crijns H, Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJ. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med*. 2009;360:668–678.
55. Page RL, Connolly SJ, Crijns HJ. Rhythm- and rate-controlling effects of dronedarone in patients with atrial fibrillation: insights from the ATHENA trial. American Heart Association Scientific Sessions, November 8–12, 2008, New Orleans, La (abstract 4097).
56. Sanofi-aventis. DIONYSOS Study Results Showed the Respective Profiles of Dronedarone and Aminodarone. http://en.sanofi-aventis.com/binaries/20081223_dionysos_fe_en_en_tcm28–23624.pdf. December 23, 2008.
57. Kowey PR, Singh BN. Dronedarone in patients with implantable defibrillators. Heart Rhythm 2004: 25th Annual Scientific Sessions of the Heart Rhythm Society, May 19–22, 2004, San Francisco, Calif: Late-breaking clinical trials oral presentation.