A review of the pharmacokinetics, electrophysiology and clinical efficacy of dronedarone

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The results of major clinical trials and advances in pharmacologic and nonpharmacologic therapies are continuing to alter treatment approaches for both atrial and ventricular arrhythmias. Originally developed as an antianginal medication, amiodarone serves as the most effective antiarrhythmic drug in the treatment of both atrial and life-threatening ventricular arrhythmias. However, amiodarone has complex pharmacokinetics and is associated with serious extracardiac side effects, partially due to the presence of an iodine moiety. With a better understanding of the mechanisms of arrhythmias and antiarrhythmic drugs, new antiarrhythmic agents are currently under development with the hope that they will be more effective and safer than currently available drugs. One such drug that might potentially fulfill this hope is dronedarone. This amiodarone-like compound lacks the iodine moiety, and is similar in structure and electrophysiologic mechanisms of action to amiodarone, to date no evidence of liver, thyroid or pulmonary toxicity has been reported. Three clinical trials demonstrate efficacy in suppressing recurrences of atrial fibrillation and there is also evidence of a rate-slowing benefit during atrial fibrillation/flutter. However, the Antiarrhythmic trial with DROnedarone in Moderate-to-severe congestive heart failure Evaluating morbidity Decrease (ANDROMEDA) study, performed in patients with left ventricular dysfunction, demonstrated excess noncardiac mortality in patients treated with dronedarone. Although effective in the treatment of atrial fibrillation, the future of this novel amiodarone-like drug remains uncertain until further clarification of the excess mortality in heart failure patients is better studied.

Cardiac arrhythmias are a major cause of morbidity and mortality. The current approach to arrhythmia management is the result of major randomized controlled trials. Antiarrhythmic drugs are used for front-line therapy to manage atrial and ventricular arrhythmias. Early clinical experience with antiarrhythmic drugs shows the potential of these agents to be both anti- and pro-arrhythmic. The Cardiac Arrhythmia Suppression Trial (CAST) [1] and the Survival With ORal D-sotalol (SWORD) [2] trial demonstrate that antiarrhythmic drug-provoked proarrhythmia could increase mortality in postinfarction patients from some class IC antiarrhythmic drugs, such as flecainide and encaidine and a ‘pure’ class III drug, D-sotalol. Trials such as the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) [3], Pharmacologic Intervention in Atrial Fibrillation (PIAF) [4], and RAtio Control versus Electrical cardioversion (RACE) [5] raised the issue that rate control may be an alternative and safer front-line approach to treating atrial fibrillation, instead of using antiarrhythmic drugs to maintain sinus rhythm. Even though these trials show either strategy of rate or rhythm control is acceptable, there is general agreement that therapy must be individualized, and the choice is currently based on the safety profile of the antiarrhythmic drug [6–8]. Maintenance of sinus rhythm will continue to be the best alternative for some patients. However, currently available antiarrhythmic drugs are only effective 50% of the time in maintaining sinus rhythm for 1 year, except amiodarone which is effective approximately 65% of the time [9–15]. In addition, many of these drugs are associated with subjective adverse events, end-organ toxicity and significant proarrhythmic potential. Thus, the search continues for safer, better tolerated and more effective antiarrhythmic drugs.

During the past decade, trials such as the Canadian Trial of Atrial Fibrillation (CTAF) [16], European Myocardial Infarct Amiodarone Trial (EMIAT) [17], Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) [18], Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) [19] and the Congestive Heart Failure Survival Trial of Antiarrhythmic Therapy (CHF-STAT) [20], have show amiodarone to be effective in the treatment of atrial and ventricular arrhythmias, have a low proarrhythmic potential and demonstrated no excess mortality in patients with left ventricular...
Amiodarone consists of a benzofurane ring coupled to a p-OH-benzene structure substituted with two iodine molecules and a diethyl-ethanolamine side chain. It is the prototype multichannel antiarrhythmic that has similar effects to drugs in all four Vaughan Williams classes; amiodarone inhibits:

\[ \text{The inward } N\text{a}^+ (I_{Na}), \text{the slow inward } L\text{-type Ca}^{2+} (I_{Ca-L}) \text{ current} \]

\[ \text{The rapid component of the delayed rectifier current} \ (I_{Kr}) \]

\[ \text{The muscarinic receptor-operated } K^+ \text{ current} \ (I_{K(Ach)}) \]

\[ \text{And the } N\text{a}^-\text{ activated } K^+ \text{ current} \ (I_{K(Na)}) \]

\[ \text{A} \times \text{N} \times \text{N} \times \text{N} \]

Chronic treatment with amiodarone results in electrophysiological changes in the heart that are similar to hypothyroidism. There is also structural similarity between amiodarone and thyroid hormones. One possibility for this action is induction of an altered thyroid state by releasing iodine in the body after drug ingestion, an effect that is independent of the molecular structure of amiodarone. The other possibility independent of iodine is direct inhibition of the cardioselective T3 nuclear receptor by amiodarone or its metabolite desethylamiodarone, creating a hypothyroid state at the cellular level [24,25]. Unfortunately, it is the iodine present on the benzene ring which is responsible for some of amiodarone’s dose-related toxicity resulting in drug discontinuation in 8 to 40% of patients [26,27] due to extracardiac side effects such as, ocular and pulmonary toxicity, peripheral neuropathy, and thyroid and hepatic dysfunction.

Overview of the market
Presently, there is an unmet need of antiarrhythmic drugs with similar effectiveness and non-proarrhythmic properties, like amiodarone, without the associated extracardiac side effects, drug–drug interactions and the ability to use such a drug in a wide range of patient populations with and without structural heart disease.

Due to the fact that our knowledge and understanding of the mechanisms of atrial and ventricular arrhythmias has greatly increased, new drugs are being developed that target specific channels likely responsible for a specific arrhythmia. Drugs early in their clinical development with unique effects include piboserod (5-HT4 receptor antagonist); tedisamil (intravenous IKr blocker); RSD-1235 and AVE 0118 (atrial selective potassium inhibitors); azimilide (IKr and IKs blocker) ZP-123 (which facilitates conduction in the gap junction) and CVT-510 (long-acting A1 adenosine antagonists).

Introduction to the compound
Dronedarone is an antiarrhythmic drug, from Sanofi–Synthelabo, that shows promise. This drug is similar in efficacy and structure to amiodarone demonstrating all Class I–IV properties of the Vaughan Williams classification (Box 1). This amiodarone-like compound, without the iodine moiety, appears to have efficacy in the suppression and control of rate in atrial fibrillation/flutter without evidence of end-organ toxicity seen with amiodarone.
Dronedarone (SS33589; N-[2-butyl-3-[4-(3-dibutylaminopropoxy)benzoyl]-benzofurane-5-yl]methanesulfonamidehydrochloride) is a noniodinated benzofurane derivative structurally related to amiodarone (Figures 1A & 1B). Knowledge of the electrophysiological properties of this drug is the result of multiple basic studies comparing the acute and chronic effects of both dronedarone and amiodarone.

**Pharmacodynamics**

*In vivo* experiments in anesthetized dogs comparing the acute electrophysiologic effects of dronedarone and amiodarone show they are both very similar. This observation comes from the similar changes seen in the sinus cycle length (CL), atrium-His (AH) interval, Wenckebach CL (WCL), atria, atrioventricular node, and ventricular refractory periods, (atrial effective refractory periods [AERPs], atrioventricular effective refractory periods [AVNERPs], and ventricular effective refractory periods [VERPs]).

Dronedarone at 2.5 mg/kg i.v. is able to slow the CL by 21% (p < 0.01), prolong the WCL by 44% (p < 0.001), AH interval by 24% (p < 0.01), and atrial effective refractory periods, atrioventricular effective refractory periods [AVNERPs], and ventricular effective refractory periods [VERPs]).

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Initial results from Sun and colleagues show dronedarone to have similar electrophysiologic effects at the cellular level after both acute and chronic treatment to amiodarone [29]. The results of acute treatment with dronedarone in concentrations ranging from 1 to 10 µmol/l show shortening of the action potential duration at 50% (APD<sub>50</sub>) and 90% (APD<sub>90</sub>) in a dose-dependent manner during stimulation at 300- to 1200-ms cycle lengths. The upstroke dV/dt (<i>V</i><sub>max</sub>) during stimulation at a cycle length of 900 ms showed a decrease in a dose-dependent manner similar to the effect seen during chronic treatment with dronedarone. The significant findings of this study show dronedarone to have similar chronic effects as amiodarone after oral treatment with the drug for 3 weeks at dosages of 50 mg/kg and 100 mg/kg for both drugs compared with vehicle only. Comparison of the drug’s effects on RR, QT, and QTc intervals to control show a significant increase (p < 0.0001 for all). The ventricular APD<sub>50</sub> and APD<sub>90</sub> are increased by 20 to 49% as a function of dose and stimulation cycle length (p < 0.0001). The <i>V</i><sub>max</sub> decreases by amiodarone 100 mg/kg (p < 0.0001) and dronedarone 100 mg/kg (p < 0.01). In another study, Sun and colleagues compared the acute and chronic effects of dronedarone and amiodarone on the transmembrane action potentials and effective refractory period (ERP) in isolated rabbit atrial muscle preparations [30]. Both drugs had similar acute and chronic effects after treatment with dronedarone and amiodarone at 50 mg/d or 100 mg/d for 4 weeks. The results after chronic treatment show an increase in steady-state APD<sub>90</sub> for dronedarone at 100 mg/d of 19.0% compared with control (58±4 ms control versus 69±2 ms dronedarone, p < 0.01), and amiodarone at 100 mg/d of 17.2% compared with control (68±3 ms amiodarone, p < 0.01). The results also show an increase in ERP with dronedarone (49±6 ms control versus 53±4 ms dronedarone; p < 0.0; 63±6 ms amiodarone; p < 0.01). The response to stimulation by frequencies from 1–8 Hz after chronic treatment also shows an increase in APD<sub>90</sub> and ERP for both drugs at all frequencies. However, the <i>V</i><sub>max</sub> shows a frequency-dependent decrease after chronic treatment with both drugs. In contrast, acute analysis showed a decrease in steady-state APD<sub>90</sub> for both drugs (61±6 ms control versus 53±4 ms dronedarone, p < 0.05; 52±6 ms amiodarone, p < 0.05), ERP (50±5 ms control versus 44±4 ms dronedarone, p < 0.05; 43±6 ms
amiodarone, p < 0.05) and $V_{\text{max}}$ (188 ± 9 V/s control versus 182 ± 11 V/s dronedarone, p < 0.05: 182 ± 11 V/s amiodarone, p < 0.05). The findings of both of these studies on isolated rabbit heart preparations show dronedarone and amiodarone to have similar acute and chronic electrophysiological effects. Although chronic dronedarone creates a hypothyroid state at the cellular level in cardiac myocytes, it does not show the same effect on the thyroid as amiodarone. This finding suggests that dronedarone may not cause an altered thyroid state or the iodine-related extracardiac complications noted with amiodarone. However, some of the chronic beneficial electrophysiological effects seen with dronedarone might be due to its structural similarity with thyroid hormone resulting in cardioselective inhibition of T₃ receptors in cardiac muscle.

Varró and colleagues, in a comparison of dronedarone and amiodarone, reported similar acute but strikingly different chronic electrophysiological effects [31]. Acutely, 10 µM of dronedarone versus amiodarone resulted in moderate lengthening of the papillary muscle APD at (1 Hz from 239.6 ± 5.3 ms to 248 ± 5.3 ms, p < 0.05), but shortening of the APD in the Purkinje fibers (at 1 Hz from 309.6 ± 11.8 ms to 287.1 ± 10.8 ms, p < 0.05). This study also examined the ability of acute effects of both drugs to reduce the incidence of early and delayed after depolarizations evoked by 1 µM of dofetilide and 0.2 µM strophanthidine in Purkinje fibers. By means of patch-clamp analysis, dronedarone markedly inhibits the ($I_{\text{Ca-L}}$) current (76.5 ± 0.7%, p < 0.05) and the ($I_{\text{Kr}}$) current (97 ± 1.2%, p < 0.05) in ventricular myocytes but did not show significant effect on $I_{\text{K1}}$, $I_{\text{Ks}}$ and $I_{\text{Na}}$. The significant finding of this study is the difference between the chronic effects of dronedarone and amiodarone. Treatment with oral dronedarone $2 \times 25$ mg/kg/d for 4 weeks, unlike treatment with oral amiodarone 50 mg/kg/d for 4 weeks, did not significantly lengthen the QTc interval of the electrocardiogram or the ADP in papillary muscle. A small but significant use-dependent decrease in $V_{\text{max}}$ with chronic dronedarone is seen (suggestive of a Class I action). This study supports previous reports that iodine in the molecular structure is probably needed to cause the characteristic amiodarone-like chronic electrophysiological changes. Furthermore, the interaction with thyroid metabolism or the thyroid hormone receptor is not seen with dronedarone or its metabolite N-debutyldronedarone [M Delbruyère (2001) Unpublished Results], but chronic treatment with amiodarone and accumulation of its metabolite N-desethylamiodarone is partially responsible for the hypothyroid state at the cellular level. Although the acute effects of dronedarone are in agreement with results of Sun and coauthors, the chronic effects are in sharp contrast to their findings [29,30]. Explanation for this discrepancy is not possible solely on the basis of differences in drug dosage, experimental conditions or species.

In addition to blockade of $I_{\text{Ks}}$ and $I_{\text{Ca-L}}$ currents in isolated canine hearts, Gautier and colleagues also demonstrate the ability of dronedarone to simultaneously block both components of the delayed rectifier potassium current, $I_{\text{K}}$ ($IC_{50} \leq 3$ µM) and $I_{\text{Ks}}$ ($IC_{50} \sim 10$ µM), as well as $I_{\text{Ca-L}}$ ($IC_{50} = 0.18$ µM) and inward rectifier potassium $I_{\text{Kr}}$ ($IC_{50} \geq 30$ µM) currents in guinea-pig cardiomyocytes. The results of this study also show dronedarone (3, 10 and 30 µM) decreases dV/dt max ($I_{\text{Na}}$) current in a concentration- and frequency-dependent manner. At the same time, blockade of these ion channels by dronedarone minimally decreases APD₉₀ and APD₅₀ but does not change APD₇₀ and APD₉₀ of papillary muscle [32]. These observations suggest the AP lengthening effect due to outward current ($I_{\text{Ks}}$, $I_{\text{K}}$, and $I_{\text{Kr}}$) block is offset by the AP-shortening effect due to inward current ($I_{\text{Ca-L}}$ and $I_{\text{Na}}$) block by dronedarone. The results of this trial are similar to the results showing the acute electrophysiological effects of dronedarone in canine ventricular muscle by Varró and colleagues.

In addition to dronedarone blocking $I_{\text{Na}}$, $I_{\text{Ca-L}}$, $I_{\text{K}}, I_{\text{Ks}}$, and $I_{\text{Kr}}$ currents, two studies also demonstrated that that dronedarone can block ($I_{\text{K(Ach)}}$) current in a concentration-dependent manner in guinea-pig atrial cells and rabbit sinoatrial nodal myocyte [33,34]. In guinea-pig atrial cells, carbachol-induced ($I_{\text{K(Ach)}}$) activation is blocked effectively at all potentials by dronedarone with an IC₅₀ of approximately 10 nM, which is approximately 100 times lower than that of amiodarone (IC₅₀ ≥ 1 µM). Activation of ($I_{\text{K(Ach)}}$) by intracellular loading with GTP-γS (100 µM) is also blocked 28 and 58% at 0.01 and 0.1 µM of dronedarone respectively [33]. Dronedarone is also effective in blocking ($I_{\text{K(Ach)}}$) in single cells isolated from sinoatrial node tissue of rabbit hearts, after external perfusion in concentrations (0.001 – 1 µM) with an IC₅₀ of 63 nM. The data also show dronedarone effectively blocks ($I_{\text{K(Ach)}}$) despite intracellular...
perfusion with GTP-γ-S. Both studies show dronedarone acts directly on ($I_{K_{Ach}}$) channels and/or GTP-binding proteins and not on the muscarinic M2 receptor. Furthermore, these studies identify dronedarone as a selective ($I_{K_{Ach}}$) blocker because its $IC_{50}$ value is over one order of magnitude lower than those reported for Ca$^{2+}$ and K$^+$ currents [35].

A study by Thomas and coauthors further supports the evidence that the Class III antiarrhythmic action of dronedarone is blockade of $I_{K_r}$ and $I_{K_s}$ by using the molecular correlates of these channels in a heterologous Xenopus oocyte expression of hERG (analogous to $I_K$) and KvLQT1/minK (analogous to $I_K$). This study shows dronedarone can block current carried by human ether-a-go-go related gene (hERG)-expressing oocytes with an $IC_{50}$ of 9.2 µM (with maximal observed inhibition of 85.2%), but the effect of dronedarone on currents carried by oocytes expressing KvLQT1/minK is a weaker block (33.2% reduction with 100 µM drug concentration) [36]. The results of this study provide a molecular mechanism for the Class III antiarrhythmic action of dronedarone by demonstrating that dronedarone is an antagonist of cloned HERG potassium channels with additional inhibitory effects on KvLQT1/minK currents at high drug concentrations. This action is similar to the acute actions of amiodarone on HERG channels ($IC_{50}$ of 9.8 µM with maximal inhibition of 62.8%) [36].

Hodeige and coauthors demonstrated the Class II antiarrhythmic effects of dronedarone and amiodarone by their ability to block α- and β-adrenoceptors in anesthetized atropinized dogs. Both dronedarone and amiodarone are able to inhibit adrenaline α-adrenoceptor-mediated increase in blood pressure to a similar extent. Blockade of isoprenaline β$_1$-adrenoceptor-mediated increase in heart rate is more pronounced with amiodarone than dronedarone (heart rate elevation reduced by 39%, p < 0.001 with 10 mg/kg dronedarone and by 52%, p < 0.01 with 10 mg/kg amiodarone), but blockade of isoprenaline β$_2$-adrenoceptor-mediated decrease in blood pressure is more pronounced with dronedarone than amiodarone (mean blood pressure decrease reduced by 69%, p < 0.01 with 10 mg/kg dronedarone and by 31%, p < 0.05 with 10 mg/kg amiodarone) [37].

The previous animal experiments show a frequency-dependent decrease of $dV/dt_{max}$ by dronedarone, implying a change in the depolarizing $I_{Na}$ current. Lalévée and colleagues noted only a modest direct effect of dronedarone and amiodarone on the $I_{Na}$ current in voltage-clamped human atrial myocytes. Amiodarone inhibits $I_{Na}$ modestly at 3 µM (41 ± 11%) and significantly at 30 µM (80 ± 7%), but dronedarone is able to inhibit $I_{Na}$ significantly at only 0.3 µM (23 ± 10%) and completely (97 ± 4%) at 3 µM [38]. This data shows that the acute inhibitory effects of dronedarone on $I_{Na}$ are similar to but more potent than amiodarone, and that the presence of iodine on the drug–molecule structure is not required for this Class I effect on $I_{Na}$ channel.

Several trials also show similarities between dronedarone and amiodarone in disease states. Early investigation testing the antiarrhythmic potential show both dronedarone and amiodarone to be effective against arrhythmia induction both during ischemia and reperfusion in rats. This study shows dronedarone significantly reduces the incidence of ventricular fibrillation during ischemia from 80 to 30% (p < 0.05) at 3 mg/kg i.v., and eliminates mortality at 10 mg/kg i.v. In contrast, amiodarone at 10 mg/kg i.v. only eliminates mortality during ischemia from 60 to 0% (p < 0.01), while no significant effect on mortality is seen with 3 mg/kg i.v. On reperfusion (after a 5-minute period of ischemia), dronedarone significantly reduces the incidence of mortality from 90 to 20% (p < 0.01) at 1 mg/kg i.v. and eliminates mortality at 3 and 10 mg/kg i.v. No significant effect on reperfusion-induced ventricular fibrillation (VF) and mortality is seen with 1 and 3 mg/kg i.v. of amiodarone, but 10 mg/kg i.v. completely eliminates reperfusion-induced VF and mortality. One adverse outcome in this trial with dronedarone at 10 mg/kg i.v. is the induction of atrioventricular (AV) block during ischemia and reperfusion in approximately 20% of the rats [39]. The results of this trial show dronedarone exhibits significant antiarrhythmic properties, is effective against arrhythmias arising as a result of myocardial ischemia, and also as a result of sudden reperfusion of the ischemic myocardium in rats. Furthermore, dronedarone displays effects similar to amiodarone but is approximately ten times more potent.

In another study using isolated rat hearts, Rochetaing and colleagues examined the acute effects of dronedarone and amiodarone on ischemic contracture, APD duration, and ventricular tachycardia during reperfusion after global low-flow ischemia. Ischemic contracture is a surrogate index for ischemic injury. By a Class
III-independent action, both drugs given during ischemia are shown to attenuate ischemic contracture, and facilitate mechanical function recovery at the end of reperfusion in a bell-shaped concentration–response relationship. This study also shows that dronedarone and amiodarone during reperfusion can suppress ventricular tachycardia in direct correlation with the ability to antagonize the APD lengthening that occurs during ischemia [40].

The antiarrhythmic effects of dronedarone and amiodarone on ischemic pig hearts once again show dronedarone to be more potent than amiodarone in suppressing ventricular arrhythmias. This study shows a reduction of ventricular fibrillation from 90% in the control group to 30% (p < 0.05) with dronedarone 1.25 mg/kg, to 10% (p < 0.001) with 2.5 mg/kg, and to 20% (p < 0.01) with 5 mg/kg versus 40% and 50% (p = NS) with 10 mg/kg and 20 mg/kg of amiodarone respectively. Both dronedarone, especially at the two higher doses, and amiodarone significantly reduce the incidence of ventricular tachycardia (VT) and the number of premature ventricular complexes (PVCs) per minute [41].

To detect ventricular repolarization abnormalities with acute and chronic dronedarone and amiodarone, anesthetized dogs with complete chronic AV block are ideal because they have a high sensitivity for acquiring torsade de pointes. In this study, different effects occur after acute treatment with dronedarone (2 × 2.5 mg/kg/10 min i.v.) and chronic treatment with dronedarone (20 mg/kg, b.i.d). Shortening of ventricular repolarization (QT, 435 ± 60 ms to 360 ± 55 ms; left ventricular action potential duration (LVAPD), 395 ± 75 ms to 325 ± 60 ms; p < 0.05) is seen with dronedarone i.v., but the idioventricular rhythm and ventricular effective refractory period remain similar (VERP, 225 ± 30 ms to 230 ± 30 ms).

Acute and chronic amiodarone produce similar results. However, chronic dronedarone increases the QT, and idioventricular rhythm cycle length. This study shows dronedarone intravenously able to suppress ectopic beats, early after depolarizations, and acquired time-dependent polarization by means of reducing and homogenizing ventricular repolarization [42].

Pharmacokinetics & metabolism

Administration of dronedarone can be intravenous or by mouth. There is only 15% bioavailability because of extensive first-pass hepatic metabolism through CYP4503A4 system. Similar to amiodarone, there is a two- to threefold increase in serum concentration if dronedarone is taken with food. With twice-daily dosing the drug reaches steady-state levels in 5 to 7 days. The elimination half-life of dronedarone is 24 h [43].

Clinical efficacy

From the results showing the multichannel effects of dronedarone causing Class I–IV antiarrhythmic effects, it is expected that this amiodarone-like drug might maintain the beneficial effects seen with amiodarone while avoiding the toxic extracardiac effects of iodine. Based on dronedarone’s basic electrophysiologic effects, one would expect the drug to have antiarrhythmic efficacy in suppressing premature ventricular complexes and ventricular tachycardia/fibrillation. However, insufficient human data are available at this time related to the drug’s ventricular antiarrhythmic potential. The majority of human antiarrhythmic data comes from trials assessing the efficacy of dronedarone in suppressing atrial fibrillation. The Dronedarone Atrial Fibrillation study after Electrical cardioversion (DAFNE) is the first prospective randomized trial evaluating the efficacy and safety of dronedarone. In this dose-ranging study, placebo or dronedarone 400, 600, or 800 mg twice daily is randomly given to 199 patients with atrial fibrillation more than 3 and less than 365 days, and followed for 6 months to measure the primary end point of time to atrial fibrillation recurrence (Table 2). In comparison with placebo, the dosing of dronedarone 400 mg twice daily significantly prolongs the time to recurrence of atrial fibrillation (median time 60 days in the dronedarone group versus 5.3 days in the placebo group, p < 0.001; relative risk reduction = 55%; CI, 28% to 72%) [44]. The higher doses show no significant difference in the primary end point. In this study, no patient

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<tr>
<th>Placebo</th>
<th>400 mg b.i.d</th>
<th>600 mg b.i.d</th>
<th>800 mg b.i.d</th>
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<tr>
<td>N</td>
<td>48</td>
<td>54</td>
<td>54</td>
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<tr>
<td>Median days/NSR</td>
<td>5.3</td>
<td>59.9</td>
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<td>Time to AF recurrence (RR)</td>
<td>0.45 (0.28–0.72)</td>
<td>0.95 (0.62–1.45)</td>
<td>0.68 (0.42–1.11)</td>
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§22.6% discontinued drug due to GI adverse side effects
AF: Atrial fibrillation; DAFNE: Dronedarone Atrial Fibrillation study after Electrical Cardioversion; GI: Gastrointestinal; NSR: Normal sinus rhythm
RR: Relative risk.
discontinued the placebo; however, patients in the 800, 1200, and 1600 mg dronedarone groups discontinued the drug at a rate of 3.9, 7.6, and 22.6%, respectively. Most frequently, patients discontinued the drug because of gastrointestinal side effects (diarrhea, nausea, and emesis). Importantly, dronedarone at the 800 mg dose did not produce any extracardiac (serious) side effects, or proarrhythmia. Interestingly, this study did not show a clearcut dose–response pattern often seen with other new class III agents even after adjusting for differences in baseline characteristics and concomitant therapies. DAFNE demonstrated that dronedarone, at a dose of 400 mg twice daily, was safe and effective in this small study population, although patients with low ejection fraction are not included.

Two other pivotal Phase III trials assessing the efficacy of dronedarone in the maintenance of sinus rhythm in patients with atrial fibrillation/flutter are now complete (Table 3). The results were first presented at the European Society of Cardiology Congress 2004, and again during the 2004 scientific sessions of the American Heart Association [45]. The Australian–American–African trial with DronedarONEIn atrial fibrillation or flutter patients for the maintenance of Sinus rhythm (ADONIS) and the EUROpean trial in atrial fibrillation or flutter patients Receiving Dronedarone for the maintenance of Sinus rhythm (EURIDIS) are both blinded placebo-controlled identical-design efficacy trials randomizing patients in a 2:1 ratio of either placebo or dronedarone 400 mg twice daily. Patients had a history of atrial fibrillation/flutter during the previous 3 months and had to be in sinus rhythm for at least 1 h prior to randomization. In the two trials, 1237 patients were randomized to either dronedarone or placebo (612 in EURIDIS, and 625 in ADONIS).

In EURIDIS, dronedarone prolonged the median time to recurrence of atrial fibrillation/flutter from 41 days in the placebo group to 96 days (RR = 0.784, p = 0.0138). In ADONIS, the median time to recurrence lengthened from 59 days in the placebo group to 158 days in the dronedarone group (RR = 0.725, p = 0.0017). Dronedarone also showed a significant effect on symptomatic recurrence, significantly slowing the ventricular response rate by about 12 to 15 beats per minute (bpm) compared with placebo (p < 0.001) [45]. The adverse events in both groups were similar (62.8% on placebo versus 67.4% on dronedarone) including mortality (0.7% on placebo versus 1% on dronedarone). The withdrawal rate due to adverse drug effects was also similar between the two groups (6.1% on placebo versus 9.5% on dronedarone). In the two studies involving 828 patients taking dronedarone, no cases of torsades de pointes, thyroid or lung dysfunction were reported. Both of these Phase III trials show dronedarone is effective in maintaining sinus rhythm in patients with atrial fibrillation/flutter and controlling rate during atrial fibrillation/flutter recurrence. The safety profile in this population is similar to placebo without the propensity for proarrhythmia or (serious) extracardiac side effects.

The safety of dronedarone, in moderate-to-severe congestive heart failure, was assessed in the ANtiarrhythmic trial with DROnedarone in Moderate-to-severe congestive heart failure Evaluating morbidity Decrea se (ANDROMEDA). trial. ANDROMEDA was a double-blind, placebo-controlled study evaluating dronedarone (800 mg daily) in high-risk patients with CHF and ventricular dysfunction. On January 16, 2003, after enrolling only 627 patients of the 1000 planned, the data safety monitoring board, following an interim safety analysis recommended, and the steering committee stopped the trial due to the issue of a potential excess risk of death in patients treated with dronedarone [46]. In-depth analysis and a clear interpretation of the present data did not show differences in baseline characteristics or concomitant medications as the cause for the excess mortality. The cardiac mortality in both dronedarone and placebo groups were similar (dronedarone, 36%; placebo, 35%) including cardiac arrest events (dronedarone, 2.0%; placebo, 1.4%), cardiac failure events (dronedarone, 14.0%; placebo, 11.5%) and arrhythmia events (dronedarone, 3.3%; placebo, 4.6%) [46]. This data cannot

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<th>Table 3. ADONIS/EURIDIS [45].</th>
<th>Placebo</th>
<th>400 mg b.i.d</th>
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<tr>
<td><strong>N</strong></td>
<td>146/155</td>
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<tr>
<td><strong>Median days/ NSR</strong></td>
<td>59/41</td>
<td>158/96</td>
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<tr>
<td><strong>Time to AF recurrence (RR)</strong></td>
<td>0.72 (p = 0.0017)/ 0.78 (p = 0.0138)</td>
<td></td>
</tr>
<tr>
<td><strong>Discontinued due to adverse drug effect</strong></td>
<td>6.1%</td>
<td>9.5%</td>
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</table>

**ADONIS**: Australian–American–African trial with DronedarONE in atrial fibrillation or flutter patients for the maintenance of Sinus rhythm; **EURIDIS**: EUROPean trial in atrial fibrillation or flutter patients Receiving Dronedarone for the maintenance of Sinus rhythm; **NSR**: Normal sinus rhythm; **RR**: Relative risk.
exclude the possibility of chance as an explanation for the excess noncardiac mortality.

**Regulatory affairs**
Although the above trials are complete, dronedarone is not currently on the market or approved for use in any country.

**Conclusion**
This drug evaluation identifies the current need for new drugs to add to our armamentarium in the treatment of atrial and ventricular arrhythmias. The efficacy of amiodarone shows us that this multichannel-blocking drug is a good prototype for the development of similar drugs. However, alterations in the molecule need to be made to minimize end-organ toxicity. For this reason, Sanofi–Synthelabo developed a noniodinated benzofuran derivative called dronedarone. The similarities between dronedarone and amiodarone are confirmed by many preclinical animal studies. This drug is shown on a cellular level to act on multiple channels. Clinical trials using this drug demonstrates it is effective in the treatment and management of atrial fibrillation. An important finding with this drug is the low proarrhythmic potential and no elimination of side effects due to iodine. The results of the ANDROMEDA suggest that dronedarone may have some unknown noncardiac adverse effects in patients with congestive heart failure. Thus, even though efficacy in suppressing atrial fibrillation has been demonstrated in two prospective placebo-controlled trials, the excess mortality noted in ANDROMEDA may limit the drug’s commercial viability.

**Future perspective**
Dronedarone, the ‘son of amiodarone’ as Dr Hohnloser states, is no wonder drug. Even though ADONIS and EURIDIS show dronedarone to be effective in prolonging the time to recurrence of atrial fibrillation/flutter, the cumulative recurrence rate for these two arrhythmias is high (77% with placebo and 66% with dronedarone). Many questions need to be answered about this drug. Long-term safety data, better dose response curves, efficacy in ventricular arrhythmias, more studies assessing drug and implantable cardioverter-defibrillator interactions with dronedarone, and explanation of the safety in CHF patients is needed. Although no formal application exists yet, Sanofi Aventis is discussing approval of dronedarone with both European and US regulatory authorities. It is not certain what the future for dronedarone is, but with the recent removal of several drugs from the market and strict criteria used by the FDA in approving antiarrhythmic drugs, combined with the results of ANDROMEDA it is unlikely this drug will be approved in the USA without some limitation of which patient populations can be treated with the drug. Whether dronedarone is approved commercially or not, there are other amiodarone analogs in development that may one day become the ‘next wonder drug’.

**Information resources**
Clinical information about dronedarone can be found at www.theheart.org and information regarding the latest news about dronedarone and press release of ANDROMEDA can be found at www.sanofi-synthelabo.com.

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**Executive summary**
- Current management of atrial and ventricular arrhythmias is the result of many large randomized controlled trials.
- Amiodarone is the most effective antiarrhythmic drug presently available for the treatment of both atrial and ventricular arrhythmias.
- Because of the serious extracardiac side effects of amiodarone there is a need for drugs with the same antiarrhythmic profile as amiodarone, but without the serious extracardiac side effects.
- Dronedarone is a multichannel antiarrhythmic drug with similar electrophysiologic effects as amiodarone without the serious extracardiac side effects.
- The efficacy trial Dronedarone Atrial Fibrillation study after Electrical Cardioversion (DAFNE) shows dronedarone to be safe and effective in patients without left ventricular dysfunction.
- Two prospective, placebo-controlled efficacy trials, Australian–American–African trial with DronedarONe In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm (ADONIS) and EUROpean trial in atrial fibrillation or flutter patients Receiving Dronedarone for the maintenance of Sinus rhythm (EURIDIS), show dronedarone to be effective in suppressing recurrences of atrial fibrillation.
- Antiarrhythmic trial with DrOnedarone in Moderate-to-severe congestive heart failure Evaluating Morbidity Decrease (ANDROMEDA) shows excess noncardiac mortality with dronedarone in patients with congestive heart failure (CHF) and the study had to be prematurely terminated by the data and safety monitoring board.
Bibliography

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.


- Detailed study of the electrophysiology of dronedarone at cellular, tissue and intact heart levels in the dog.


- A detailed study of cellular electrophysiology of dronedarone in the guinea-pig.


- Provides the first direct investigation on a molecular basis of repolarizing K+ current pharmacology of dronedarone in human atrial myocytes.


- Study providing direct evidence for action of dronedarone on cardiac sodium channels.


- Clinical trial showing dronedarone prevents atrial fibrillation relapses after cardioversion.


- Important Phase III trials showing effectiveness of dronedarone in management of atrial fibrillation.


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