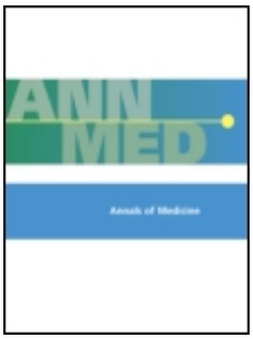

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DRUG FOCUS ARTICLE

Dronedarone: An overview

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. Until recently, a rhythm control strategy for AF has been limited by drug toxicity and side-effects, and landmark AF trials have shown that such a strategy is not superior to a rate control one. New antiarrhythmic drugs, free of undesired effects, would enhance the rhythm control strategy, with the possibility of sinus rhythm restoration and maintenance.

One of the promising drugs recently approved for clinical use is dronedarone. This drug has amiodarone-like antiarrhythmic and electrophysiological properties, despite it having a modified structure and lacking an iodine moiety. Thus, dronedarone lacks amiodarone's organ toxicity (including adverse thyroid and pulmonary effects). The efficacy of dronedarone has been investigated in several clinical trials, proving its effect in the prevention of AF recurrence, rate control in paroxysmal/persistent and permanent AF, reduction of cardiovascular hospitalization or death from any cause, and others. Indirect comparisons with amiodarone, as well as one head-to-head study of the two drugs, indicate that the relative safety of dronedarone may be at a cost of its lower antiarrhythmic efficacy compared with amiodarone.

Key words: *Amiodarone, atrial fibrillation, dronedarone, SR33589*

Introduction

Atrial fibrillation (AF), the most frequent clinical arrhythmia, remains a serious medical problem and a key challenge for cardiologists. The presence of AF confers a significant mortality and morbidity, due to stroke, thromboembolism, heart failure, impaired quality of life, and recurrent hospitalizations.

Treatment of AF patients poses a great challenge for any clinician and can broadly be divided into two major therapeutic strategies, that is, rate and rhythm control (1,2). A rhythm control strategy is meant to maintain sinus rhythm by all available means, including cardioversion, pharmacotherapy with antiarrhythmic agents and beta-blockers, and catheter ablation; while a rate control strategy aims at control of the ventricular rate in AF by the use of rate-limiting drugs such as digoxin, beta-blockers, and calcium channel antagonists, as well as pacing and/or ablation of the atrioventricular (AV) junction (1). All AF patients are considered for appropriate antithrombotic therapy, based on their thromboembolic risk (3) and irrespective of the type of AF recurrence (paroxysmal, persistent, permanent) (1–3).

A rate control strategy is not inferior to the rhythm control one in terms of survival (4,5), including patients with impaired left ventricular systolic function (6). Stable sinus rhythm may bring

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Key message

- Dronedarone is a very promising drug that has recently been approved for clinical use in atrial fibrillation.

symptomatic improvement (7). In an ancillary analysis of the predictors of survival in the largest rate versus rhythm control trial, the presence of sinus rhythm was associated with decreased risk of death, but this was offset by an increase in mortality by the use of antiarrhythmic agents to prevent AF recurrence (8). Thus, new and safe antiarrhythmic agents could redefine the balance towards more use of a rhythm control strategy.

Also, there may be some specific subsets of patients among those with AF who might particularly benefit from stable sinus rhythm. For example, heart failure patients have a higher incidence of AF, but—on the other hand—they are also at greater risk associated with antiarrhythmic therapy, and some agents cannot even be safely used in that population (9–11).

All of the above drive the search for new antiarrhythmic drugs (12,13). Safe and effective drugs might bring new solutions for patients in whom the currently available therapy is contraindicated or brings side-effects. The major disadvantage of the most effective drug against AF—amiodarone (10)—is its extra-cardiac toxicity. Therefore, analogues of amiodarone, with its efficacy preserved and toxicity reduced, are desired and searched for (10,11).

In this article we provide an overview of dronedarone, with a short discussion of its electrophysiology and particular focus on the clinical trial data.

Search strategy

We performed a search of the databases MEDLINE (1966–May 2010), EMBASE and SCOPUS (1965–May 2010), and DARE (1966–2010). Additionally, abstracts from national and international cardiovascular meetings were studied. Where necessary, the relevant authors of these studies were contacted to obtain further data. The main search terms were: arrhythmia, dronedarone, SR33589, atrial fibrillation, and treatment.

Mechanism of action

Dronedarone (SR33589) is a synthetic analogue of amiodarone. One of its modifications with respect to amiodarone is removal of the iodine moiety. The aim of the development of dronedarone was to introduce a drug as effective as its parent compound but lacking thyroid and pulmonary toxicity. The half-life period of dronedarone is 1–2 days, which is significantly shorter than that for amiodarone (30–55 days) (14). This is due to less tissue accumulation, resulting from decreased lipophilicity. The steady state of plasma concentration is reached after 14 days of administration (15). Some of the available data concerning the molecular and electrophysiological mechanism of action and preclinical efficacy of dronedarone are discussed below.

Molecular mechanism(s)

Dronedarone, initially referred to as SR33589 (or N, N-dibutyl-3-[4-([2-butyl-5-methylsulphonamido] benzofuran-3-ylcarbonyl)phenoxy]propylamine), is chemically related to amiodarone (16,17). Dronedarone was developed for the treatment of AF and atrial flutter, but its efficacy—presumed on the basis of preclinical research—comprises AF and flutter, other atrial tachycardias, and also ventricular arrhythmias (18). That presumption will have to be confirmed in appropriately designed clinical trials, to be applicable in human arrhythmias (17,18).

Dronedarone has electrophysiological properties similar to amiodarone (18). Although developed to be a class III antiarrhythmic agent, dronedarone exhibits properties of all four antiarrhythmic Vaughan-Williams classes. Dronedarone has multiple channel effects, including inhibition of Na, K, and Ca currents. It also inhibits the acetylcholine-activated K current in atrial and sino-atrial nodal tissue. Dronedarone is also an antagonist of alpha- and beta-adrenergic receptors (19). It decreases the maximum rate of rise of action potential (dV/dt) but does not significantly change the duration of the action potential. Physiological effects, as well as ionic and molecular mechanisms of action of dronedarone, are summarized in Table I.

Certain preclinical study results address the issue of dronedarone toxicity (20). Although these data cannot be translated directly into toxicity in human use, they are still important. In one such study, dronedarone did not affect plasma levels of T3, T4, and rT3, except a decrease in T4 level at the highest tested dose. In comparison, the administration of amiodarone caused a dose-dependent increase of the T4/T3 ratio and the level of rT3 (20). In another study, the effects of metabolites and analogues of amiodarone on alveolar macrophages were studied and compared with dronedarone (among others) (21). It was established that dronedarone has greater toxicity than amiodarone towards alveolar macrophages. Any association of that finding with clinical action is not known. To date, data concerning

Table I. Physiological effects, ionic and molecular mechanisms of action of dronedarone.

Ref.	Model	Ionic currents affected	Physiological effects
(38)	Guinea-pig papillary muscle	I(Kr), I(Ks), I(K1), and I(Ca(L)) inhibited	- decrease of dV/dt max of the action potential in a concentration- and frequency-dependent manner - no change of resting potential - action potential amplitude decreased only at highest concentration of the drug - reduction of papillary muscle contraction - reduced shortening of ventricular myocytes
(17)	Anaesthetized and conscious dogs	I(Na), I(Kr), I(Ks), I(K1), and I(Ca(L)) inhibited	- decrease of dV/dt max of the action potential - no change of action potential duration
(39)	Guinea-pig atrial cells	I(K(ACh)) inhibited	- dronedarone inhibited the I(K(ACh)) current by inhibition of the channel itself and its GTP-binding proteins - effect of dronedarone more potent than of amiodarone
(20)	Rat heart	Cardiac beta-adrenoceptor inhibited	- *in vitro*, SR 33589, like amiodarone, was characterized as non-competitive beta-adrenoceptor antagonist - chronic treatment led to a down-regulation of the beta-adrenoceptor
(17,20,39,40)	Anaesthetized and conscious dogs		- in anesthetized dogs: o both dronedarone and amiodarone inhibited alpha-adrenoceptor stimulation o dronedarone inhibited beta1 receptors significantly, but less than amiodarone o dronedarone inhibited beta2 receptors more than amiodarone did - in conscious dogs: o both dronedarone and amiodarone inhibited an isoprenaline-induced rise of heart rate; the extent of that action was similar for both drugs
(41)	Normal and infarcted rat hearts	I(K) or Isus inhibited, small increase in I(to)	- dronedarone increased action potential duration in normal hearts, but it did not further increase APD that was already prolonged by myocardial infarction - no proarrhythmic effect of the drug - reduction of ventricular premature beats in infarcted hearts
(42)	Rat hearts—ischaemia and reperfusion		- dronedarone reduced the incidence of ventricular fibrillation induced by ischaemia - it reduced mortality during reperfusion and reduced the incidence of ventricular fibrillation - 20% of animals exhibited atrioventricular block at the highest tested dose of dronedarone (10 mg/kg), which was not observed at lower doses
(21)	Acute coronary occlusion in anaesthetized pigs		- dronedarone reduced the occurrence of ventricular arrhythmias (ventricular premature beats, ventricular tachycardia, and fibrillation) during ischaemia
(43)	Rabbit hearts		- dronedarone increased RR, QT, and QTc intervals - it prolonged ventricular action potential duration at 50% and 90% repolarization in a dose-dependent and cycle length-dependent manner - effects of dronedarone were more significant than those of amiodarone - V(max) was decreased by both drugs, and both drugs slowed the sino-atrial node automaticity
(31)	Canine hearts, dronedarone versus amiodarone	I(Ca(L))	- 4-week oral administration of the drug: o small V(max) block, less significant than that caused by amiodarone - acute intravenous infusion: o moderate prolongation of action potential duration in papillary muscle and its shortening in Purkinje fibres - both drugs reduced early and late after-depolarizations
(40)	Isolated canine atria		- dronedarone caused a less marked increase of action potential duration, effective refractory period, diastolic threshold of excitation, and V(max) than amiodarone - dronedarone was also less efficient in termination of AF and prevention of AF recurrence

ACh = acetylcholine; AF = atrial fibrillation; APD = action potential duration; Ca = calcium; GTP = guanosine triphosphate; K = potassium; QT = QT interval as measured in ECG; QTc = value of QT corrected with respect to heart rate; RR = RR interval as measured in ECG.

pulmonary toxicity of dronedarone are lacking. In available clinical studies no pulmonary fibrosis was reported, but the follow-up period might be insufficient to reveal any late toxicity (20,21). Long-term clinical use will hopefully clarify that issue. The promising effect of dronedarone on ventricular and/or ischaemia-induced arrhythmias has not yet been sufficiently confirmed in humans (20,21).

Clinical evidence

Dronedarone has been released for clinical use in the United States and in the European Union, based on the results of several clinical trials. The most relevant issues emerging from those studies are discussed below. More detailed information can be found in Table II.

DAFNE

DAFNE (Dronedarone Atrial FibrillatioN study after Electrical cardioversion) (15) was a dose-ranging, phase II trial, which aimed to establish an optimal dosing regimen for further research. Dronedarone was most effective at a dose of 800 mg daily. After 6 months of therapy 35% of patients in the 800 mg dronedarone group were in sinus rhythm, compared with 10% in the placebo group, although the authors admit that the relapse rate is unusually high compared with other studies of anti-arrhythmic drugs. There was no difference in the cardioversion success rate among the groups receiving dronedarone (at any dose) or placebo. The authors report no proarrhythmic effects of the drug, and no episodes of torsade de pointes (TdP) were observed. No side-effects affecting thyroid function, vision, or respiratory system were noted. Gastrointestinal disturbances were the main side-effects. QT prolongation due to drug therapy was observed only in the 1,600 mg dronedarone group. Discontinuation of the drug was reported in 3.9%, 7.6%, and 22.6% of patients in the 800 mg, 1,200 mg, and 1,600 mg drug groups, respectively. Gastrointestinal disturbances (diarrhoea, nausea, emesis) were the most significant reasons for drug discontinuation. An interesting finding in the DAFNE study was the lack of dose-dependency of the therapeutic effects of dronedarone. Only the 800 mg daily dose turned out to be significantly effective in comparison with placebo, an effect that may be attributable to some extent to the higher side-effect rate and discontinuation rate in the higher dose groups. In contrast, the acute conversion rate to sinus rhythm caused by dronedarone was dose-dependent (15,22).

ANDROMEDA

The ANDROMEDA study (Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease) (23) investigated the ability of dronedarone to reduce the composite primary end-point of death from any cause or hospitalization for heart failure. Reduction of hospitalization rate for heart failure and mortality benefit due to reduction of arrhythmias were the expected outcomes (23). What is worth noting is that a history of arrhythmia, including AF, was not mandatory in that study. The study was prematurely terminated for safety reasons, due to significant excess mortality in patients receiving the active drug compared with placebo, with no significant difference between groups in terms of the primary end-point. Further analyses revealed that the risk of death associated with active treatment with dronedarone was increased in patients with impaired left ventricular function. Deaths in the dronedarone group were mainly attributable to the worsening of heart failure (23). The drug also caused a small increase in the number of hospitalizations due to heart failure, which further supports the link between use of the drug and deterioration of circulatory insufficiency. An additional finding of the study is an increase in plasma creatinine concentration. That side-effect has been observed and reported in most clinical trials involving dronedarone. It has been proven in healthy volunteers that this effect may be attributable to an impaired mechanism of creatinine transport (cation transporters) (23). Dronedarone influences the renal handling of creatinine and N-methylnicotinamide, which are both cations, and it does not affect the glomerular filtration rate (measured using sinistrin clearance) or renal plasma flow and anion secretion (measured using para-aminohippurate clearance) (23,24). The effect is transient, is directly associated with drug administration, and resolves with drug discontinuation. It is not associated with drug toxicity, but it means that dronedarone may cause interactions with cationic agents. All in all, the results of the ANDROMEDA study led to the conclusion that dronedarone should not be administered in patients with severe heart failure and impaired left ventricular systolic function (23,24).

ADONIS/EURIDIS

ADONIS (American-Australian-African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm) and EURIDIS (European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm) were two identically

Table II. Summary of clinical trials of dronedarone.

Trial	Inclusion criteria	Patients included	Intervention	Primary end-point	Results	Secondary end-points	Results
DAFNE (15)	Persistent AF (72 h–12 months), rhythm converted to sinus with ECV if no SR after 5–7 days of therapy	270 pts, in 199 SR was restored, 21–85 years of age	Dronedarone (800 mg, 1200 mg, 1600 mg daily) or placebo for 6 months	Time to first documented recurrence of AF	Dronedarone (800 mg daily) increased time to first recurrence compared to placebo (60 versus 5.3 days; $P = 0.001$)	1. Spontaneous conversion of AF following randomization 2. VR in case of recurrence 3. Incidence of side-effects 4. Pharmacokinetics	1. 5.8%–14.8% of patients experienced (dose-dependent) effect, compared to 3.1% in the placebo group 2. Reduced in a dose-dependent manner 3. GI side-effects were dominant, discontinuation rate 3.9%–22.6% in the dronedarone group 4. Steady state reached on day 14 after randomization
ADONIS/ EURIDIS (14)	At least 1 episode of AF during 3 months before enrolment, at least 1 h in SR before randomization	828 pts dronedarone, 409 pts placebo	Dronedarone 800 mg daily or placebo	Time to first recurrence of AF or flutter	Time to first recurrence prolonged in the drug group (116 days, 53 days in placebo group)	1. Symptoms related to AF 2. Mean VR at first recurrence	1. Rate of symptomatic recurrences was reduced 2. Reduced in the drug group compared with placebo ($P < 0.001$)
ANDROMEDA (23)	Severe symptomatic heart failure (NYHA III or IV, or paroxysmal nocturnal dyspnoea), LWMI no more than 1.2	627 pts	800 mg of dronedarone daily or placebo, median F-U time 2 months	Death from any cause or hospitalization for worsening heart failure	Prematurely terminated for safety reasons (excess mortality in dronedarone group): HR = 2.13; 95% CI = 1.07–4.25; $P = 0.03$. No difference in primary end-point	1. Death from all causes 2. Hospitalization for CV causes 3. Hospitalization for worsening CHF 4. Occurrence of AF/AFl 5. Arrhythmic death 6. SCD	1. Increased 2. Increased 3. N/a 4. N/a 5. N/a 6. N/a
ATHENA (25)	Paroxysmal or persistent AF (at least 1 record within 6 months) and at least one additional risk factor for death: • age > 70 years • AH treated with at least 2 drugs • DM • Previous stroke, TIA, or peripheral embolism • LA diameter ≥50 mm • LVEF no more than 40% SR was restored according to guidelines	4628 pts	Dronedarone 800 mg daily or placebo, at least 12 months of follow-up (F-U); mean time of F-U 21 months.	First hospitalization due to CV events or death	Reduced in the drug group (31.9% versus 39.4% in the placebo group)	1. Death from any cause 2. Death form CV causes 3. Hospitalization due to CV events	1. No difference 2. Reduced (2.7% versus 3.9% in the placebo group; $P = 0.03$) 3. Reduced (29.3% versus 36.9% in the placebo group; $P < 0.001$)

ERATO (28)	Permanent AF (>6 months), average VR ≥80 bpm	174 pts, 85 received dronedarone, 89 - placebo	Dronedarone 800 mg daily or placebo for 6 months	Change in mean VR on the 14th day of therapy in comparison to the base-line value	Reduction of mean VR by 11.7 bpm ($P<0.0001$) compared to placebo	1. Mean VR after 4 months of therapy 2. VR at submaximal exercise on the 14th day 3. VR at maximal exercise on the 14th day 4. Safety and tolerability	1. Reduced (8.8 bpm compared to placebo; $P<0.001$) 2. VR reduced in the drug group by 25.6 bpm with respect to base-line ($P<0.0001$) 3. VR reduced in the drug group by 27.4 ($P<0.0001$) bpm with respect to base-line 4. GI disturbances, increase in digoxin levels
DIONYSOS (29)	Persistent AF with indications for cardioversion and antiarrhythmic treatment	504 pts: 249 received dronedarone, 255 amiodarone	Head-to-head study, dronedarone or amiodarone for 6 months	Time to first AF recurrence or premature drug discontinuation due to intolerance or lack of efficacy	End-point was reached by 75.1% patients receiving dronedarone and 58.8% on amiodarone ($P<0.0001$)	Safety end-point: side-effect rate	Dronedarone did not reduce the main safety end-point, but after exclusion of GI side-effects there was a significant difference in the remaining side-effects in favour of dronedarone

AF = atrial fibrillation; AH = arterial hypertension; CHF = congestive heart failure; CV = cardiovascular; DM = diabetes mellitus; ECV = electrical cardioversion; GI = gastrointestinal; LWMI = left ventricular motion index; pts = patients; SCD = sudden cardiac death; SR = sinus rhythm; VR = ventricular rate.

designed trials (14). The former was conducted in the United States, Canada, Australia, Africa, and Argentina, while the latter took place in Europe. Both studies assessed the efficacy of dronedarone compared with placebo (14). Patients previously treated with amiodarone were allowed to enter the study immediately after discontinuation of that drug. Heart rhythm was monitored transtelephonically at pre-specified time points and if symptoms occurred (14).

In both studies dronedarone increased the time to arrhythmia recurrence and reduced the recurrence rate after 12 months of follow-up. Results for the pooled data from both studies were as follows: median time to recurrence 116 days (dronedarone) and 53 days (placebo); recurrence rate 64.1% of patients in the dronedarone group and 75.2% in the placebo group (HR 0.75; 95% CI 0.65–0.87; $P<0.001$) (14,15). Similar efficacy in end-point reduction was shown in subanalyses of various subgroups of patients (e.g. with structural heart disease, hypertension, and left atrial enlargement) (14,15). Dronedarone also reduced the mean ventricular rate during recurrence of arrhythmia (14,15). Most recurrences were symptomatic, and the pattern of symptoms was unchanged by treatment.

In a *post-hoc* analysis (23) the rate of hospitalization or death in combined data was 22.8% in the dronedarone group and 30.9% in the placebo group (HR 0.73; 95% CI 0.57–0.93; $P=0.01$). The side-effect profile in those studies was mostly consistent with that previously reported (14,15,23).

Unfortunately, the study included patients after recent discontinuation of amiodarone (14,15). The published data do not give specific information concerning the time between treatment with amiodarone and enrolment in the study. We only learn that approximately 30% of patients had previously been treated with amiodarone (14,15). Therefore, in our opinion, it is impossible to exclude bias resulting from the amiodarone wash-out period overlapping the period of treatment with dronedarone, especially if the time periods to the first recurrence of arrhythmia in the ADONIS/EURIDIS studies are not longer than the maximum elimination time of amiodarone.

ATHENA

The ATHENA trial (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg b.i.d. for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation or Flutter) investigated the capacity of dronedarone compared with placebo to reduce the

Table III. Clinical efficacy of dronedarone.

Clinical effect	Source of data
1. Prolongation of the median time to AF recurrence after sinus rhythm restoration with cardioversion.	DAFNE, ADONIS/EURIDIS (14,15,22,23)
2. Dose-dependent spontaneous conversion into sinus rhythm.	DAFNE (15,22)
3. No influence on the success rate of cardioversion.	DAFNE (15,22)
4. Dose-dependent reduction of ventricular rate in the case of recurrence of AF.	DAFNE (15,22)
5. Reduction of the percentage of patients in whom AF recurred after 12 months of treatment.	ADONIS/EURIDIS (14,15,23)
6. Reduction of the percentage of patients with symptomatic arrhythmia recurrence.	ADONIS/EURIDIS (14,15,23)
7. Reduction of hospitalization rate due to cardiovascular events or mortality in patients with paroxysmal and persistent AF/AFl.	ATHENA (25–27,35)
8. Reduction of hospitalization rate due to cardiovascular causes.	ATHENA (25–27,35)
9. Reduction of the percentage of patients with first hospitalization due to cardiovascular causes.	ATHENA (25–27,35)
10. Reduction of cardiovascular mortality.	ATHENA (25–27,35)
11. Reduction of mean ventricular rate in the course of permanent AF, both the mean daily rate (after 14 days and 4 months of treatment) and exercise rate (after 14 days of treatment).	ERATO (28)
12. Recurrence of AF or premature drug discontinuation is more frequent with dronedarone than amiodarone.	DIONYSOS (29)
13. More AF recurrence but a trend towards less drug discontinuation with dronedarone than amiodarone.	DIONYSOS (29)

AF = atrial fibrillation; AFl = atrial flutter.

primary end-point defined as first hospitalization due to cardiovascular events or death (25). Secondary end-points were death from any cause, death from CV causes, and hospitalization due to CV events. The study included patients with paroxysmal or persistent AF and additional risk factors for death. During the recruitment period the inclusion criteria were changed to increase median risk of death in the study population. Altogether 3.9% of the patients enrolled had left ventricular ejection fraction (LVEF) less than 35%, while 11.9% had LVEF less than 45%. Chronic heart failure with symptoms in New York Heart Association (NYHA) class II was present in 17.1% of patients and NYHA III in 4.4% of patients (25).

Dronedarone reduced the rate of primary end-point occurrence. The effect was consistent in a subgroup analysis of patients, subdivided according to age, sex, LVEF, and presence of AF/atrial flutter (AFl), but such analyses were not predefined in the study protocol (25).

As for secondary end-points, dronedarone did not influence overall mortality, but reduced the rate of death from CV causes and the end-point of first hospitalization due to CV causes (25). The difference was mainly attributable to the reduction of hospitalizations due to AF, and there was no difference in the rate of hospitalization for heart failure or ventricular arrhythmias (25).

The rate of treatment discontinuation was similar in both groups (25). Patients in the active treatment group experienced more side-effects of treatment, such as bradycardia, QT interval prolongation, diarrhoea, nausea, rash, and increased plasma creatinine level. No difference was noted related to the function of the thyroid gland or respiratory tract. One episode of TdP was observed in a patient in the drug group; nevertheless, the average risk of arrhythmic death was lower in that group (25).

The results of the study (25), and specifically the reduction of primary end-point in the population with moderate heart failure, proved the efficacy and safety of dronedarone in that population, as the authors claim. Nonetheless, the use of dronedarone remained contraindicated in patients with severe heart failure, such as the study group of ANDROMEDA, in which there is doubt regarding the safety of the drug use. In the ATHENA study the results in patients with heart failure were similar to the results for the whole study population. That issue was further analysed in a *post-hoc* analysis of the ATHENA study results (26). Among 4,628 patients included in the study there were 209 patients with stable chronic heart failure, NYHA class II/III, and LVEF $\leq$ 40 (114 of them were randomized to receive placebo and 95 to receive dronedarone). The history of heart failure and impaired left ventricular function was not reflected in any change of study outcomes in that group. In those patients there was no excess mortality due to treatment with dronedarone (HR for dronedarone for all-cause mortality 0.71; 95% CI 0.33–1.55), but there was a trend towards the reduction of primary end-point (HR 0.78; 95% CI 0.52–1.16), while the primary

end-point was significantly reduced with dronedarone in the whole study population. The profile of adverse effects was also similar in heart failure patients compared with the whole study population. The median time from randomization to first hospitalization due to NYHA IV symptoms was almost the same for heart failure patients receiving placebo and dronedarone (227 versus 228 days). The drug did not cause excess mortality due to pump failure, which might have been presumed based on the results of the ANDROMEDA study. A conclusion of the study and *post-hoc* analysis would be that dronedarone may be safely administered in patients with stable heart failure in NYHA class II and III but may be dangerous for patients with recent episodes of decompensated heart failure and therefore should be avoided in that particular group (25,26).

The ATHENA study (27) also provided data for a very valuable analysis of stroke occurrence in the study population. No antiarrhythmic drug had been previously reported to reduce the incidence of stroke in AF patients, even in the case of effective reduction of the arrhythmia burden. There is even some evidence that assignment to the rate control strategy does not necessarily mean a reduction of the risk of stroke (27). Dronedarone is the first antiarrhythmic drug with evidence that might suggest its potential to reduce the incidence of stroke (27). That *post-hoc* analysis included all strokes that had been observed in the ATHENA study. Groups of patients randomized to receive dronedarone or placebo were not different in terms of risk factors for stroke (no difference in the base-line CHADS2 score) or the use of anticoagulation and antiplatelet therapy. According to that analysis, dronedarone reduced the risk of stroke from 1.8% annually to 1.2% (HR 0.66; 95% CI 0.46–0.96; $P = 0.027$) (27). The rate of ischaemic and haemorrhagic strokes analysed separately was not significantly influenced. That effect of the active treatment was especially marked in patients with CHADS2 score ≥ 2 ($P = 0.03$). When the base-line characteristics were analysed in search of predictors of the time to stroke, three factors were found to increase the risk of stroke: prior stroke or TIA, age (each year of age increased the risk of stroke by 4%), and randomization to placebo compared with dronedarone. The authors speculate that the mechanism for the reduction of the risk of stroke might include: suppression of AF, slight fall in blood pressure observed with dronedarone, or decrease of mean heart rate in the case of AF recurrence. However, that analysis was not pre-specified in the study design and should therefore be considered with reservations (27). Further investigation of that issue is certainly needed.

ERATO

In previous studies of dronedarone (DAFNE, ADONIS/EURIDIS) it was found that the drug reduces the ventricular response rate during AF in the case of paroxysmal/persistent AF recurrence (14). The aim of the ERATO study (Efficacy and safety of dRonedArone for The cOntrol of ventricular rate during atrial fibrillation) was to evaluate the influence of dronedarone on ventricular rate during the permanent form of AF, when added to standard rate control therapy (28). Primary outcome was the change in mean ventricular rate on the 14th day of therapy in comparison to the base-line value. Secondary outcomes included mean ventricular rate after 4 months of therapy, as well as the ventricular rate during submaximal and maximal exercise, and also safety and tolerability of the drug (28). Special attention was paid not to change the dosage of other rate-lowering drugs during the first 14 days of treatment, until the primary outcome day.

Dronedarone caused a significant reduction of mean ventricular rate compared with the base-line value, and also compared with placebo. What is more, dronedarone showed an additive effect to the typically used rate-lowering drugs such as beta-blockers, calcium channel blockers, and digoxin, and the additive effect was observed with each of those drugs. The significant effect of dronedarone was also maintained after 4 months of treatment (28).

The ventricular response during submaximal and maximal exercise was also reduced during therapy with dronedarone, which did not influence exercise capacity.

No incidents of TdP or sustained ventricular tachyarrhythmias were observed, the discontinuation rate was not increased in the active study group, but dronedarone again caused an increase of the serum creatinine level (28). Importantly, dronedarone caused an increase of digoxin concentration by 41.4% on average, but the percentage of patients with digoxin concentration outside the therapeutic range was not increased when compared with the placebo group. No influence of dronedarone on the international normalized ratio value (INR) was reported in patients on oral anticoagulation therapy. The ERATO study confirmed the potential of dronedarone as a rate control agent, both in paroxysmal/persistent (which had been reported before) and permanent AF (in the ERATO study) (28).

DIONYSOS

DIONYSOS (29) was a head-to-head study of dronedarone versus amiodarone to compare their efficacy and safety. The composite primary end-point

Table IV. Electrophysiological effects of dronedarone observed in preclinical and clinical trials.

	Rabbit hearts (Sun et al.) (43)	Dog hearts (Varro et al.) (31)	Dog hearts (Manning et al.) (32)	DAFNE (15,22)	ADONIS/EURIDIS (14,15,23)	ERATO (28)	ATHENA (25–27,35)
HR	reduction		reduction	reduction by 7.2–11.1 bpm, dose-dependent	reduction by 6.8%		bradycardia
WCL			prolongation				
AH			prolongation				
HV			no change				
AERP/AVNERP/VERP			prolongation				
PR			prolongation	prolongation by 13.4–28.4 ms, dose-dependent			
QRS				no change	no change		
QT	prolongation			variable (prolongation, subsequent shortening)	prolongation by 23.4 ms		prolongation
QTc	prolongation	no change			prolongation by 9.0 ms		
VR at arrhythmia recurrence				reduction by 17.8 bpm (average), dose-dependent	reduction by 12/15.2 bpm reduction by 10%/13% compared to placebo		
VR in the course of FAC, 24 h average						reduction	
VR in the course of FAC at submaximal exercise						reduction	
VR in the course of FAC at maximal exercise						reduction	

AERP = effective refractory period of the atria; AVNERP = effective refractory period of the atrioventricular node; FAC = chronic atrial fibrillation; HR = heart rate; PR = PR interval as measured in ECG; QT = QT interval as measured in ECG; QTc = value of QT corrected with respect to heart rate; VERP = effective refractory period of the ventricles; VR = ventricular rate; WCL = cycle length corresponding to the point of Wenckebach.

was AF recurrence or premature drug discontinuation due to intolerance or lack of efficacy. More patients reached the end-point in the dronedarone group than in the amiodarone group (HR 1.59; 95% CI 1.28–1.98; $P < 0.0001$) (29). The difference in the composite end-point was attributable to AF recurrence (more frequent for dronedarone), but the discontinuation rate was lower for dronedarone. AF recurred after electrical cardioversion in more patients treated with dronedarone, but the acute success rate of cardioversion was similar for both drugs (29). Dronedarone did not cause a significant reduction of the main safety end-point, defined as thyroid, hepatic, pulmonary, neurological, skin, ocular, and gastrointestinal side-effect rate, or premature study drug discontinuation due to any adverse event (29). Gastrointestinal events were more frequent in the dronedarone group, and when those side-effects were excluded from the analysis, there was a significant decrease in favour of dronedarone of all the other events. No incidents of TdP were reported in that study. The incidence of bradycardia and QT prolongation was lower in the dronedarone group. Those results mean that dronedarone is less efficacious in terms of AF recurrence prevention when compared with amiodarone, but has a better safety profile (29).

Other evidence

The key issue associated with this new antiarrhythmic drug, i.e. efficacy and safety in comparison with amiodarone, remained unsolved until the results of the only head-to-head study became available. An attempt to compare dronedarone and amiodarone indirectly was made by the authors of a meta-analysis, which was intended to translate the results of amiodarone and dronedarone efficacy studies against placebo into a comparison of those two drugs with each other (30). According to that analysis, it was proposed that dronedarone be regarded as less efficacious than its parent compound, amiodarone. The calculated efficacy of amiodarone against placebo was significant (OR 0.12; 95% CI 0.08–0.19), as opposed to dronedarone, which did not appear to be significantly more efficacious than placebo (OR 0.79; 95% CI 0.22–1.87) (30). Amiodarone was more efficient than dronedarone (OR 0.49; 95% CI 0.37–0.63; $P < 0.001$) in prevention of AF recurrence. The calculated mortality for amiodarone was insignificantly higher than for dronedarone (OR 1.61; 95% CI 0.97–2.68; $P = 0.066$), and the rate of side-effects resulting in drug discontinuation was significantly higher for amiodarone (OR 1.81; 95% CI 1.33–2.46; $P < 0.001$) (30). The authors calculated that lower efficacy of dronedarone together with its lower toxicity would result in 228 more recurrences of AF in exchange for 9.6 fewer deaths and 62 fewer side-effects, if 1,000 patients were treated with dronedarone instead of amiodarone (30). The analysis raised some controversy (31,32), but one issue is generally agreed on: all doubts can be solved only by further direct clinical comparisons of the two drugs. The results of that analysis are consistent with the results of the DIONYSOS study in the general sense that dronedarone may be less efficacious than its parent compound, but it offers a higher level of safety (33,34).

Summary of proven clinical effects

Clinical efficacy

The available clinical evidence, including antiarrhythmic efficacy as well as some other clinical features of dronedarone, is summarized in Table III.

Electrophysiological effects

Dronedarone causes a reduction of sinus rhythm rate, prolongation of PQ, QT, and QTc intervals,

Table V. Side-effects observed during therapy with dronedarone.

Side-effect	Source of data
1. Transient increase of plasma creatinine concentration, associated directly with drug administration, resulting from impairment of tubular transporter, with no features of toxic renal damage and no reduction of glomerular filtration rate	DAFNE, ADONIS/EURIDIS, ANDROMEDA, ATHENA, ERATO, DIONYSOS (14,15,22-29,35)
2. Gastrointestinal side-effects	DAFNE, ATHENA, ERATO, DIONYSOS (14,22,25-29,35)
3. No proarrhythmia, almost no incidents of TdP (only 1 case of TdP in the ATHENA study)	DAFNE, ADONIS/EURIDIS, ERATO, DIONYSOS (14,15,22,28-29)
4. Increased mortality in patients with severe heart failure—NYHA III or IV, LWMI below 1.2 (which is consistent with LVEF below 35%)	ANDROMEDA (23)
5. Increase of digoxin concentration if administered concurrently with dronedarone	ERATO (28)

LVEF = left ventricular ejection fraction; LWMI = left ventricular motion index; NYHA = New York Heart Association; TdP = torsade de pointes.

and reduction of ventricular rate during AF (see above). The drug does not influence the duration of QRS complexes (14,15,22–29). The electrophysiological properties of dronedarone are summarized in Table IV.

Side-effects

Clinical studies of dronedarone revealed several side-effects in humans, some of which (an increase of plasma creatinine concentration and gastrointestinal disorders) were consistently recorded in several studies. Reported side-effects are listed in Table V.

In addition to side-effects observed in clinical trials, one may be concerned with the recent safety alert on the use of dronedarone, issued in the United States by the FDA. The agency received post-marketing safety data in which several cases of severe liver injury were reported during the treatment with dronedarone, including two cases of acute liver failure leading to liver transplant, in which no other aetiology could be found. Even if that condition were to be linked with the use of dronedarone, its rate would be very low, given the fact that during the period of interest around 150,000 patients filled dronedarone prescriptions in the US. Nonetheless, the FDA advised physicians to counsel the patients about the necessity to report any signs and symptoms of possible liver failure and to consider periodic hepatic enzymes screening, especially during the first 6 months of treatment.

Conclusions

Dronedarone is a new antiarrhythmic drug, with proven efficacy in prevention of AF recurrence (22–29). It may only be used to treat AF patients. The registered indication is the use of dronedarone to reduce hospitalization rate due to cardiovascular causes or mortality in patients with paroxysmal/persistent AF/AFl (as in the ATHENA study) (25–27,35). Dronedarone has some potential to terminate an on-going AF episode, but this property has not been studied as a stand-alone endpoint. Therefore, its efficacy in pharmacological cardioversion cannot be analysed (22–34). The drug has rate control properties in the course of both paroxysmal/persistent and permanent AF. It might therefore be used in both rhythm and rate control strategies of AF treatment (which is similar to amiodarone) (36,37). The risk of uncontrolled restoration of sinus rhythm in patients with permanent AF is not known. There are some analyses that question the efficacy of dronedarone, but only further clinical data in that field may bring conclusive results (22–32).

It is possible that further evidence will allow more wide-spread use of dronedarone. Particularly interesting seems to be the issue of dronedarone efficacy in ventricular tachyarrhythmias, but the available data on the use of the drug in patients with heart failure (ANDROMEDA study) (23), who constitute the main group at risk of ventricular arrhythmias and sudden cardiac death, are far from encouraging (23).

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