European Heart Journal (2003) **24**, 1481–1487

Dronedarone for prevention of atrial fibrillation: A dose-ranging study

Paul Touboul[a], Josep Brugada[b], Alessandro Capucci[c], Harry J.G.M. Crijns[d], Nils Edvardsson[e], Stefan H. Hohnloser[f]*

[a] *Division of Cardiology, Hôpital Cardiologique, Lyon, France*
[b] *Arrhythmia Unit, Cardiovascular Institute, Hospital Clinic, University of Barcelona, Barcelona, Spain*
[c] *Divisione di Cardiologia, Ospedale Civile Polichirurgico, Cantone del Cristo 29100 Piacenza, Italy*
[d] *Department of Cardiology, Academic Hospital Maastricht & Cardiovascular Research Institute, Maastricht, Netherlands*
[e] *Division of Cardiology, Sahlgrenska University Hospital, 413 45, Goteborg, Sweden*
[f] *J.W. Goethe University, Department of Cardiology, Frankfurt am Main, Germany*

Received 31 January 2002; received in revised form 5 May 2003; accepted 12 June 2003

KEYWORDS
Antiarrhythmic agents;
Atrial fibrillation;
Cardioversion

Aims Dronedarone, a benzofurane derivative without iodine substituents, shares the electrophysiologic properties of amiodarone. This study was designed to determine the most appropriate dose of dronedarone for prevention of atrial fibrillation (AF) after cardioversion.
Methods and results Patients with persistent AF were randomly allocated to 800, 1200, 1600 mg daily doses of dronedarone or placebo. The main analysis was conducted on 199/270 patients, who entered the maintenance phase following pharmacological cardioversion or, if unsuccessful, DC cardioversion. Within 6-month follow-up, the time to AF relapse increased on dronedarone 800 mg, with a median of 60 days vs 5.3 days in the placebo group (relative risk reduction 55% [95% CI, 28 to 72%] P=0.001). No significant effect was seen at higher doses. Spontaneous conversion to sinus rhythm on dronedarone occurred in 5.8 to 14.8% of patients (P=0.026). There were no proarrhythmic reactions. Drug-induced QT prolongation was only noticed in the 1600 mg group. Premature drug discontinuations affected 22.6% of subjects given 1600 mg dronedarone versus 3.9% on 800 mg and were mainly due to gastrointestinal side effects. No evidence of thyroid, ocular or pulmonary toxicity was found.
Conclusion Dronedarone, at a 800 mg daily dose, appears to be effective and safe for the prevention of AF relapses after cardioversion. The absence of thyroid side effects and of proarrhythmia are important features of the drug. Further studies are needed to better delineate the antiarrhythmic profile of the drug.

Introduction

Atrial fibrillation (AF) is the most commonly encountered cardiac rhythm disturbance accounting for 34.5% of arrhythmia-related hospital admissions in a recent US survey.[1] AF is associated with increased mortality and morbidity as highlighted by an estimated incidence of over 75.000 AF-related strokes per year in the US.[2,3]

In patients with persistent AF, electrical cardioversion is usually performed. Despite high initial success rates, this therapy is limited by the incidence of AF relapses that is as high as 70 to 80% after 12 months if no prophylactic antiarrhythmic therapy is administered.[4,5] Various class I and III antiarrhythmic drugs have been studied in controlled trials to evaluate their efficacy in maintaining sinus rhythm.[6] Overall, approximately 50% of patients on active drug therapy remained free of

* Corresponding author. Stefan H Hohnloser, MD, Department of Medicine, Division of Cardiology, J W Goethe University, Theodor Stern-Kai 7, 60590 Frankfurt, Germany. Tel.: +49-69-6301-7321; fax: +49-69-6301-7017
E-mail address: Hohnloser@em.uni-frankfurt.de (S.H. Hohnloser).

0195-668X/03/$ - see front matter © 2003 Published by Elsevier Ltd on behalf of The European Society of Cardiology.
doi:10.1016/S0195-668X(03)00321-X

recurrent AF over the first year after cardioversion. Only amiodarone showed a higher rate of efficacy as a maintenance therapy.[7,8] However amiodarone had to be discontinued due to side effects in up to 23% of patients over the course of 1–2 years according to a recent meta-analysis.[9]

Dronedarone is a benzofuran derivative structurally similar to amiodarone, which is being developed as an antiarrhythmic agent. The absence of iodine substituents and a less lipophilic character should be associated with a better tolerability. Like amiodarone, dronedarone possesses in vitro electrophysiologic characteristics of all four classes of antiarrhythmic action.[10–15] Specifically, it blocks sodium channels at rapid pacing rates, prolongs cardiac action potentials and refractoriness, and possesses Ca^{++} antagonistic properties. In addition, dronedarone shows a non-competitive antiadrenergic action.

The Dronedarone Atrial FibrillatioN study after Electrical Cardioversion (DAFNE) was a double-blind, randomized, placebo controlled trial designed to select the most appropriate dose of dronedarone for prevention of recurrent AF after successful cardioversion.

Methods

Patients with persistent AF scheduled for elective cardioversion were eligible. Effective anticoagulation had to be performed for at least 3 weeks prior to randomization. After signing informed consent, patients were allocated to one of three doses of dronedarone: 800, 1200 1600 mg daily (400, 600, 800 mg BID) or placebo. This dose range was selected based on pharmacodynamic data assessing ECG-derived parameters as surrogate endpoints for antiarrhythmic activity (heart rate, PQ-, and QT-intervals). They were continuously monitored by telemetry for at least 12 h from the beginning of treatment. If after drug exposure for 5–7 days sinus rhythm was not restored, electrical cardioversion was performed. In successfully cardioverted patients' treatment was continued for 6 months. Anticoagulation was maintained for at least 4 weeks after conversion.

Study visits in the outpatient clinic were scheduled on day 5–8, 14, 30, 60, 90, 120, 150, and 180 after randomization or at any time in case of recurrent AF or other medical problems. Transtelephonic electrocardiogram monitoring was used every day for 5 days following cardioversion, then every two weeks until day 45, and once a month up to the end of the study. Patients were also instructed to transmit their ECG in case of recurrent symptoms at any time. At each study visit, plasma samples were taken for determination of dronedarone drought levels. Five thyroid hormone assessments were planned during the follow-up.

Inclusion criteria

Patients of either sex, aged 21–85 years, with persistent AF (between 72 h and 12 months duration) for whom cardioversion and antiarrhythmic treatment was warranted were included. AF could be lone or associated with ischemic or hypertensive heart disease or dilated cardiomyopathy. Coexisting valvular anomaly did not preclude inclusion except for those patients with hemodynamically significant dysfunction at echocardiography.

Exclusion criteria

Patients with one or more of the following criteria were excluded from the study: more than two cardioversions in the last six months, acute reversible cause; atrial flutter as the presenting arrhythmia; unstable angina pectoris or recent myocardial infarction; QT interval >500 msec, or history of torsades de pointes; severe bradycardia; advanced atrioventricular block; treatment with other antiarrhythmic drugs; congestive heart failure class III or IV; left ventricular ejection fraction of less than 35%; Wolff–Parkinson–White syndrome; implanted cardioverter defibrillator.

Other criteria included profound serum potassium changes; childbearing potential; evidence of clinically relevant non-cardiac disease; contraindication to oral anticoagulation.

Statistical analysis

The primary outcome was time to first documented AF recurrence. AF recurrence was defined as an episode lasting for at least 10 min and documented by two distinct ECGs separated by the same time duration. Secondary study endpoints were spontaneous conversion of AF following randomization, heart rate in case of AF recurrence and the incidence of side effects.

Sample size calculation was based on the hypothesis of an AF recurrence rate of 67% on placebo at 6 months and 37% on at least one dose of dronedarone, a drop-out rate of 15%, a log-rank test equality of survival curves with a 5% two-sided significance level and a 80% power. This resulted in an estimated sample size of 48 patients per group.

The main analysis was conducted in the patients entering the maintenance phase after successful cardioversion. An additional analysis was also performed on the intention to treat basis in all randomized patients. A Cox's model was used taking into account the dose groups and two additional baseline covariates: presence of structural heart disease and duration of the qualifying AF episode.[16] The same approach was applied to each dronedarone group for evaluating the risk ratio with 95% confidence interval. Regarding the secondary endpoints, the trend among treatment groups was assessed using a Cochran-Armitage test for qualitative parameters, a Jonckheere-Terpstra test for ordinal parameters, an analysis of variance for continuous parameters.[17–19] Dronedarone and its main metabolite, the N-debutyl derivative, plasma concentrations were summarised by descriptive statistics.

Results

Patient characteristics

Two hundred and seventy patients were randomized in 50 centres and 11 countries. One hundred and ninety-nine patients, in whom sinus rhythm was restored, were included in the primary analysis. Patients randomized to the four groups had similar baseline characteristics as shown in Table 1.

Primary study end-point

Kaplan–Meier curves for the primary outcome are shown in Fig. 1. There was an increased time to AF relapse with dronedarone 800 mg, this effect being less apparent at higher doses. Only with 800 mg, the difference compared to placebo was statistically significant. The median time to first AF recurrence was 5.3 days in the placebo group, and 60 days in the dronedarone 800 mg group (relative risk reduction 55%, 95% CI 72–28%, P=0.001). In the two other groups, no significant change was seen indicating a

Table 1 Demographic and baseline characteristics of patients

	Placebo *n*=48	DR 800 mg *n*=54	DR 1200 mg *n*=54	DR 1600 mg *n*=43
Age (years)	65	64	63	62
Male sex (%)	79	57	70	67
Hypertension (%)	56	51	50	44
CAD[a] (%)	27	20	18	20
Valve disease (%)	50	35	31	37
Heart failure (%)	22	14	24	11
AF[b] duration (days)	82	122	92	108
Recurrent AF[b] (%)	65	50	64	54
LA[c] size (mm)	46	44	45	45
LVEF[d] (%)	56	55	53	54

[a]CAD: coronary artery disease.
[b]AF: atrial fibrillation.
[c]LA: left atrium.
[d]LVEF: left ventricular ejection fraction.

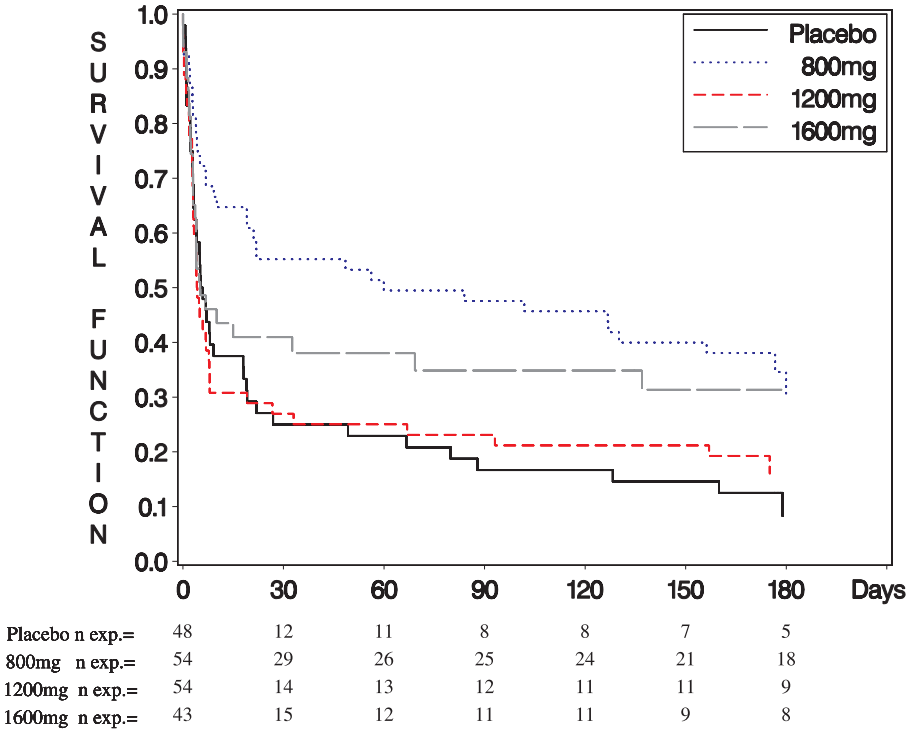

Fig. 1 Kaplan–Meier analysis of the time to first atrial fibrillation relapse according to assigned treatment. The difference in time to atrial fibrillation relapse between the dronedarone 800 mg group and the placebo group was significant (*P*=0.001); n exp.: number of exposed patients.

lack of dose effect. At 6 months, 35% of the patients treated with 800 mg dronedarone were still in sinus rhythm, as compared to 10% in the placebo group. Intention to treat analysis found similar results with time to AF recurrence of 56 days in the dronedarone 800 mg group, versus 5.3 days in the placebo group.

Conversion to sinus rhythm

The incidence of spontaneous conversion to sinus rhythm was associated with a significant dose-effect relationship (*P*=0.0261). Patients in the dronedarone 800, 1200, and 1600 mg groups exhibited 5.8%, 8.2% and 14.8% conversion rates respectively, vs 3.1% on placebo. Moreover the incidence of successful electrical cardioversion was not statistically different among groups: 77.3% (800 mg), 87.9% (1200 mg), and 76.6% (1600 mg) compared to 73.0% in the placebo group.

Ventricular rate during recurrence

At the time of first AF recurrence, dronedarone appeared to slow the ventricular response in a dose-dependent

Table 2 Adverse events leading to study drug discontinuation

	Placebo	800 mg	1200 mg	1600 mg	Dronedarone
Adverse event	*n*=66	*n*=76	*n*=66	*n*=62	*n*=204
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Total	0 (0.0)	3 (3.9)	5 (7.6)	14 (22.6)	22 (10.8)
Gastrointestinal (including diarrhea, vomiting, nausea, gastroenteritis)	0 (0.0)	1 (1.3)	1 (1.5)	7 (11.3)	9 (4.4)
General disorders (including malaise, accidental injury, anaphylactic shock, weight decrease)	0 (0.0)	0 (0.0)	1 (1.5)	4 (6.5)	5 (2.5)
Cardiac failure	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.6)	2 (1.0)
Central nervous system (dizziness)	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.6)	2 (1.0)
Dermatology	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.6)	2 (1.0)
Extrasystoles	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
QT increase	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.5)
Tachycardia supraventricular	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (0.5)
Thrombosis	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.5)

fashion. Patients receiving 800, 1200, or 1600 mg dronedarone had their ventricular rate reduced by 13.2, 19.2, and 17.8 bpm on average, respectively, compared to those on placebo (P=0.0001).

Adverse events

One death was reported in this study: this concerned a patient in the 1600 mg dronedarone group who suffered trauma due to accidental injury. Twenty-two (10.8%) dronedarone patients discontinued treatment due to adverse events. In the 800 mg, 1200 mg and 1600 mg dronedarone groups, the discontinuation rates were 3.9%, 7.6% and 22.6%, respectively (Table 2). There were no premature discontinuations in the placebo group. Most frequently, gastro-intestinal side effects (diarrhoea, nausea, vomiting) led to drug cessation. No evidence of thyroid, hepatic, neurological, ocular or pulmonary complications was found.

In terms of cardiovascular side effects, no proarrhythmic reactions, including torsades de pointes, were reported. The incidence of cardiac failure was not statistically different in patients receiving dronedarone versus placebo. ECG changes were consistent with the known electrophysiological properties of the drug. On day 5–8, heart rate was decreased by 7.2, 6.9, and 11.1 bpm in the 800, 1200 and 1600 mg groups respectively (P=0.0040). The PR-interval was lengthened by 13.4, 16.6, and 28.4 ms in the 800, 1200 and 1600 mg groups (P=0.0031). Conversely there was no clear effect on QRS duration. The QTc-interval was variably affected across visits: on day 14, after steady state was reached a mean prolongation of 39 ms was found in the 1600 mg group compared to placebo (P=0.0024), consistent with the class III properties of the drug. The proportion of patients with at least 1 QT interval >500 ms was 7.7, 6.6, 9.1, and 16.4% in the placebo, 800 mg, 1200 mg, and 1600 mg groups, respectively. Fig. 2 shows the changes in QT over time.

Pharmacokinetics

According to the drought plasma level determinations, dronedarone steady state was reached on day 14 after randomization and the steady state for the N-debutyl metabolite, on day 5-8. A 2-fold dose increase led to a 2.65- and 2.40-fold increase in dronedarone and N-debutyl metabolite concentrations, respectively. The mean metabolic ratio (N-debutyl metabolite/dronedarone) was around 0.6 whatever the dose.

Discussion

Main study findings

DAFNE is the first prospective randomized trial evaluating the efficacy and safety of dronedarone, a new antiarrhythmic agent, in patients undergoing cardioversion for persistent AF. The results demonstrate that dronedarone at a dose of 800 mg/day significantly increases the average time to first AF recurrence when compared to placebo. Importantly, at this dose, the drug was well tolerated and proved to be safe during short-term exposure. No proarrhythmic reactions were observed.

Dronedarone antiarrhythmic effect

Dronedarone at a dose of 800 mg daily-prolonged time to the first AF recurrence from an average of 5 to 60 days. This was associated with a sinus rhythm maintenance rate at 6 months of only 35%. However this figure has to be viewed in the light of the unexpectedly high relapse rate in the control group where only 10% of patients remained free from recurrent AF. The AF recurrence rate in the placebo group is much higher than that observed in recent trials evaluating new antiarrhythmic drugs.[20,21] In these two trials, 19 to 28% of placebo treated patients remained free of recurrent AF at 6 months. Accordingly, our study population appears to be at high risk for AF

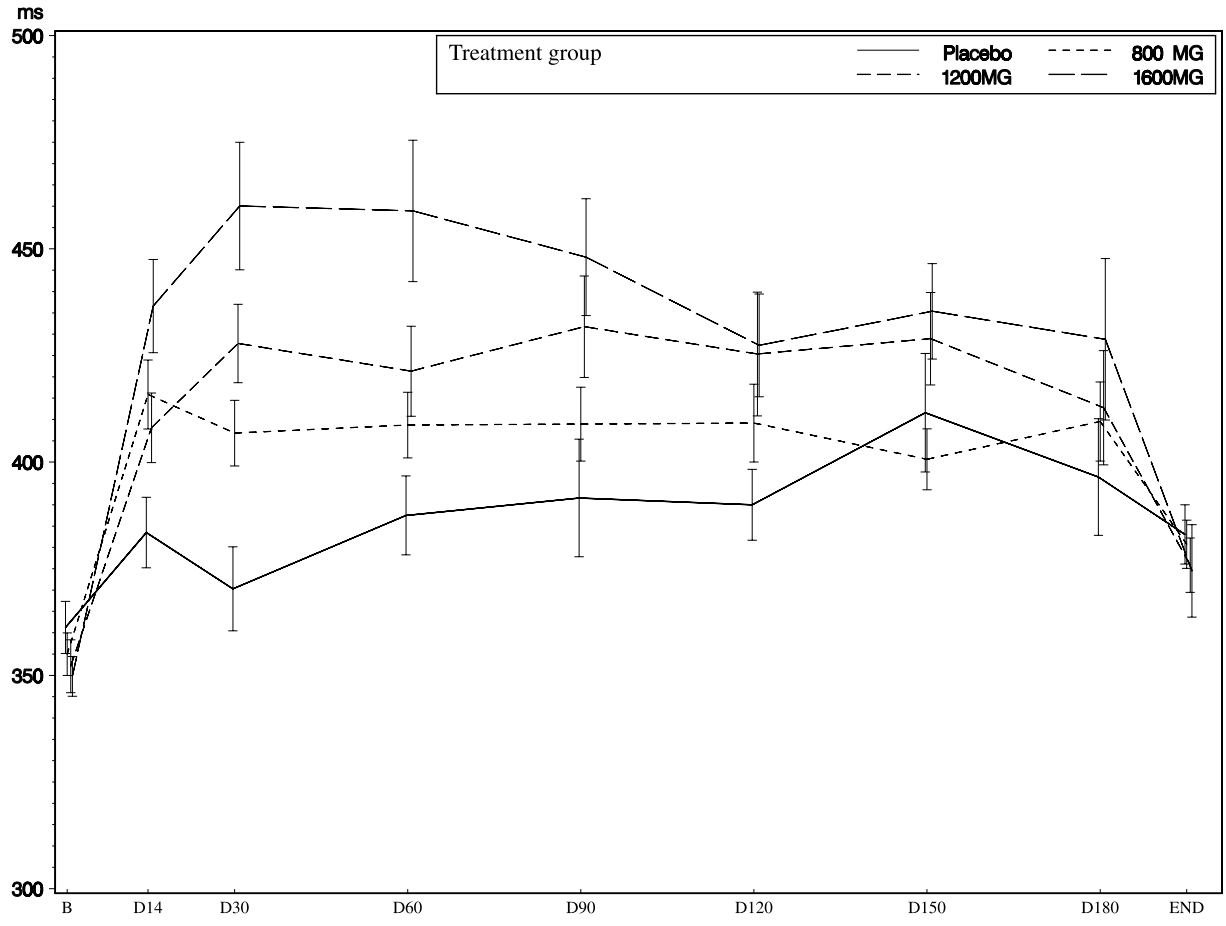

Fig. 2 Plot of QT interval (SEM) over time.

recurrences, although the precise reason for this increased atrial vulnerability remains unknown. An important methodological aspect may also account for the overall high incidence of recurrent AF within our trial. The efficacy analysis was based on transtelephonic monitoring that was symptom-activated and also used at regular follow-up visits. It can be assumed that early AF recurrences, even transient, were thus more rigorously detected.

A puzzling observation in this study was the lack of a clear-cut dose response pattern observed with other new class III agents.[20,21] Even after adjustment using Cox's model for covariates such as baseline characteristics or concomitant therapies, there was still no dose-effect relationship detectable, while the superiority of dronedarone 800 mg over placebo remained significant. This finding could also not be explained by pharmacokinetic parameters. The plasma concentrations of dronedarone and its metabolite measured in this study were in agreement with the drug characteristics as determined in healthy subjects (Clinical Investigator's Brochure, unpublished data, 2001). Another hypothesis implies the multifactor mode of action of dronedarone.[10,11,13] This would result in a bell-shaped response curve, a notion that has never been documented with dronedarone in animal models (Clinical Investigator's Brochure, Unpublished data, 2001). Finally, an important issue is the higher proportion of patient censoring in the 1200 and 1600 mg dronedarone groups, mainly due to adverse events resulting in drug discontinuations. This factor may have played a role in the absence of dose-effect relationship. Thus with dronedarone daily doses exceeding 800 mg, the reduction of the safety margin might impair the clinical benefit of the drug. However this notion is to be regarded with caution due to the limited size of the study groups.

The ability of dronedarone to convert AF to sinus rhythm was demonstrated in this trial. The drug efficacy was modest and increased with dose. The low conversion rate of dronedarone is similar to that of amiodarone or of newly developed drugs such as dofetilide.[20,22] In this setting, there was a distinct dose-response effect of dronedarone, a behaviour that appeared to be different from that seen during maintenance therapy. The most likely explanation for this discrepancy is the complex action profile of this compound. For dronedarone as for other antiarrhythmic drugs, the ion channels involved in rhythm control might be different from those contributing to pharmacological cardioversion.[23]

In case of AF relapses, patients on dronedarone had a lower heart rate as compared to those on placebo. This must reflect a slowing effect on atrioventricular

nodal conduction, a notion in accordance with the drug-induced PR prolongation during sinus rhythm.[12] Dronedarone may be a valuable adjunct to the armamentarium intended to control ventricular rate in permanent AF, and thus improve arrhythmia tolerance.

Safety

In the present study, there was no evidence for dronedarone-associated proarrhythmic reactions in any patient. In particular, no cases of torsade de pointes were observed notwithstanding the electrophysiological profile of the substance with predominant class III properties. It is noteworthy that the effect of dronedarone on the QT interval remained modest. In this respect dronedarone appears to share the benefits of amiodarone.[24] Dronedarone also proved to be hemodynamically well tolerated. However low left ventricular ejection fraction was an exclusion criterion in this trial. This overall safety profile, if confirmed in future studies including a larger and perhaps a sicker patient population, would make dronedarone particularly attractive for therapy of patients with AF in the context of structural heart disease. As expected from the absence of iodine substituents, dronedarone, unlike amiodarone, did not cause any thyroid abnormalities. This notion is of prime importance since the objective, when synthesizing dronedarone, was to get a drug sharing the properties of amiodarone, but devoid of thyroid side effects.

Conclusion

This dose-ranging study demonstrated that, in AF patients, dronedarone given at an 800 mg daily dose was effective for the maintenance of sinus rhythm following cardioversion. However further studies are required to better delineate the antiarrhythmic properties of the drug. The good safety profile associated with the 800 mg dose is an encouraging finding. The absence of thyroid side effect, as shown herein, might well be a key-factor of dronedarone's clinical future.

Acknowledgements

Sanofi-Synthelabo Recherche, France, sponsored the study. We are indebted in particular to D. Radzik, G. Frangin and A.C. Neiss who contributed to the good conduct of the study.

Appendix A

The following investigators participated in the DAFNE trial: **Investigators** — I. Blankoff, CHU Saint-Pierre, Brussels, Belgium; J.L. Wanquez, CHR de la Citadelle, Liege, Belgium; R. Tavernier, UZ Gent, Gent, Belgium; P. Brugada, OL Vrouw Ziekenhuis, Aalst, Belgium; K. Peuhkurinen, Kuoppio University Hospital, Kuopio, Finland; P. Touboul, Hôpital Louis Pradel, Lyon, France; J. Victor, CHRU Angers, France; P. Defaye, Hôpital A. Michalon, Grenoble, France; A. Da Costa, Hôpital Nord, Saint Priest en Jarez, France; S. Kacet, CHUR Lille, France; E. Quiring, SICUS, CMCO, Schiltigheim, France; A. Grand, Centre Hospitalier, Valence, France; P. Djiane, Hôpital Sainte Marguerite, Marseille, France; J. Ponsonnaille, Hôpital Gabriel Montpied, Clermont Ferrand, France; P. Blanc, Hôpital Universitaire Dupuytren, Limoges, France; S. Hohnloser, Klinikum der JW Goethe Universität, Frankfurt, Germany; J. Neuzner, Klinik Forschungsgesellschaft, Bad Nauheim, Germany; D. Kalusche, Herz-Zentrum, Bad Krozingen, Germany; K. H. Kuck, Allgemeines Krankenhaus St Georg II, Hamburg, Germany; M. Block, Augustinum Klinik, München, Germany; M. Eldar, Neufeld Cardiac Research Inst, Tel Hashomer, Israël; Z. Vered, Cardiology Institute, Zrifin, Israël; B. Strasberg, Rabin Medical Center, Petach-Tikva, Israël; P. Rizzon, Universita degli Studi di Bari, Italy; HJGM. Crijns, Academisch Ziekenhuis Groningen, The Netherlands; J.A. Kragten, Atrium Ziekenhuis, Heerlen, The Netherlands; AJM Timmermans, Medisch Spectrum Twente, Enschede, The Netherlands; FALE. Bracke, Catharina Ziekenhuis, Eindhoven, The Netherlands; A.R. Ramdat Misier, Isala Klinieken, Zwolle, The Netherlands; J.G. Meeder, ST Maartens Gashuis, Venlo, The Netherlands; DJA. Lok, St Deventer Ziekenhuizen, Deventer, The Netherlands; LHJ Van Kempen, Ziekenhuis Velp, The Netherlands; H.A., Oude Luttikhuis, Isala Klinieken, Zwolle, The Netherlands; AAM Wilde, Academisch Medisch Centrum, Amsterdam, The Netherlands; L.H. Savalle, Medisch Centrum Haaglanden, Va Dan Haag, The Netherlands; P.A. Tilon, Westfries Gasthuis, Hoorn, The Netherlands; L. Ceremuzynski, Klinika Kardiologii, Warszawa, Poland; G. Opolski, Klinika Kardiologii, Warzawa, Poland; M. Trusz-Gluza, Klinika Kardiologii, Katowice, Poland; L. Wawrzynska, Instytut Gruzlicy i Chorob Pluc, Warszawa, Poland; W. Tracz, Oddzial Kliniczny Chorob Serca i Naczyn, Krakow, Poland; M. Krzeminska-Pakula, Klinika Kardiologii, Lodz, Poland; W.J. Musial, Klinika Kardiologii, Bialystok, Poland; C. Moro, Hospital Ramon y Cajal, Madrid, Spain; J. Brugada, Hospital Clinic Universitari, Barcelona, Spain; I. Fernandez Lozano, Clinica Puerta de Hierro, Madrid, Spain; J. Alzueta Rodriguez, Hospital Clinico Universitario, Malaga, Spain; J. Almendral, Hospital Gregorio Maranon, Madrid, Spain; J. Olagüe de Ros, Hospital La Fe, Valencia, Spain; N. Pachon Rebollo, Hospital General de Asturias, Oviedo, Spain; F. Garcia-Cosio, Hospital Universitario de Getafe, Madrid, Spain; N. Edvardsson, Sahlgrenska Universitetssjukhuset, Göteborg, Sweden; P. Blomström, Thoraxcentrum-Akademiska Sjukhuset, Uppsala, Sweden; C. Sylven, Hjärtkliniken, Stockholm, Sweden; S. Jull-Möller, Universitetssjukhuset Mas, Malmö, Sweden; T. Moccetti, Cardiocentro Ticino, Lugano, Switzerland; S. Osswald Leitender Arzt Cardiologie, Basel, Switzerland; J. Fuhrer, Oberarzt Kardiologie, Bern, Switzerland; G. Noseda, Primario Medicina Interna, Mendrisio, Switzerland. **Data Safety Monitoring Board** — A. Leizorovicz (head), J. Camm, G. Schmidt. **Steering Committee** — P. Touboul (chair), J. Brugada, A. Capucci, H. Crijns, N. Edvardsson, S. H. Hohnloser, D. Radzik.

References

1. Bialy D, Lehmann MH, Schumacher DN et al. Hospitalization for arrhythmia in the United States: importance of atrial fibrillation (Abstract). J. *Am Coll Cardiol* 1992;**19**:41A.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. *Arch Intern Med* 1987;**147**:1561–4.
3. Wolf PA, Dawber TR, Thomas HE et al. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology* 1978;**28**:973–7.
4. Lundstrom T, Ryden L. Chronic atrial fibrillation. Long term results of direct current cardioversion. *Act Med Scand* 1988;**223**:53–9.
5. Coplen SE, Antman E, Berlin JA et al. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion: a meta-analysis of randomized controlled trials. *Circulation* 1990; **83**:1106–16.
6. Levy S, Breithardt G, Campbell RW et al. Atrial fibrillation: current knowledge and recommendations for management. Working Group on Arrhythmias of the European Society of Cardiology. *Eur Heart J* 1998; **19**:1294–320.
7. Chun SH, Sager PT, Stevenson WG et al. Chronic atrial fibrillation. Long term results of direct current cardioversion. *Act Med Scand* 1988;**223**:53–9.
8. Roy D, Talajic M, Dorian P et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. *N Engl J Med* 2000;**342**:913–20.
9. Vorperian VR, Havighurst TC, Miller S et al. Adverse effects of low dose amiodarone: a meta-analysis. *J Am Coll Cardiol* 1997;**30**:791–8.
10. 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**:570–6.
11. Manning AS, Bruyninckx C, Ramboux J et al. SR 33589, a new amiodarone-like agent: effect on ischemia- and reperfusion-induced arrhythmias in anesthetized rats. *J Cardiovasc Pharmacol* 1995; **26**:453–61.
12. Manning A, Thisse V, Hodeige D et al. SR 33589, a new amiodarone-like antiarrhythmic agent: electrophysiological effects in anesthetized dogs. *J Cardiovasc Pharmacol* 1995;**25**:252–61.
13. Sun W, Sarma JS, Singh BN. Electrophysiological effects of dronedarone SR 33589, a noniodinated benzofuran derivative, in the rabbit heart: comparison with amiodarone. *Circulation* 1999;**100**:2276–81.
14. Hodeige D, Heyndrickx JP, Chatelain P et al. SR 33589, a new amiodarone-like antiarrhythmic agent: anti-adrenoceptor activity in anaesthetized and conscious dogs. *Eur J Pharmacol* 1995; **279**:25–32.
15. Cosnier-Pucheu S, Guiraudou R, Rizzoli G et al. Effects of amiodarone and dronedarone in the prevention of atrial arrhythmias in guinea pig isolated heart (Abstract). *Arch Mal Cœur Vaiss* 2001;**94**:364.
16. Cox DR. Regression models and life-tables. *J R Stat Soc. (B)* 1972; **34**:187–220.
17. Armitage P. Test for linear trend in proportions and frequencies. *Biometrics* 1955;**11**:375–86.
18. Pirie W. Jonckheere tests for ordered alternatives. In: Kotz O., Johnson O, editors. Encyclopedia of statistical sciences. New York: John Wiley & Sons, Inc; 1983;**4**:315–8.
19. Steel RGD, Torrie JH. Principles and procedures of statistics. 1980, New York: MC Graw-Hill Book Co.
20. Singh S, Zoble RG, Yellen L et al. Efficacy and safety of oral defetilide in converting to and maintaining sinus rhythm in patients with chronic atrial fibrillation or atrial flutter: the symptomatic atrial fibrillation investigative research on dofetilide (SAFIRE-D) study. *Circulation* 2000;**102**:2385–90.
21. Pritchett EL, Page RL, Connolly SJ et al. Antiarrhythmic effects of azimilide in atrial fibrillation: efficacy and dose-response. Azimilide Supraventricular Arrhythmia Program 3 (SVA-3) Investigators. *J Am Coll Cardiol* 2000;**36**:794–802.
22. Hohnloser SH, Kuck KH, Lilienthal J. Rhythm or rate control in atrial fibrillation-Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomized trial. *Lancet* 2000;**356**:1789–94.
23. Nattel S, Bourne G, Talajic M. Insights into mechanisms of antiarrhythmic drug action from experimental models of atrial fibrillation. *J Cardiovasc Electrophysiol* 1997;**8**:469–80.
24. Hohnloser SH, Singh BN. Proarrhythmia with class III antiarrhythmic drugs: definition, electrophysiologic mechanisms, incidence, predisposing factors and clinical implications. *J Cardiovasc Electrophysiol* 1995;**6**:920–36.