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Patente de Invención ☒ Patente de Modelo de Utilidad ☐
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No. Solicitud Internacional PCT/IB2009/006089
Fecha de Presentación Internacional 08 Junio de 2009

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 39 a 50	09/Diciembre/2010
Reivindicaciones:	Folios 51 a 52	09/Diciembre/2010
Dibujos:	Folio 54	09/Diciembre/2010
Oposiciones:	Folios 63 a 101	Laboratorios Synthesis 19/Agosto/2011
Prioridad:	EP 08290532.4	10/Junio/2008
	US 61 060 260	10/Junio/2008

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486), y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "Dronedarona para la prevención de la cardioversión".

El problema planteado en esta solicitud consiste en la necesidad de disminuir la

necesidad de cardioversión eléctrica a pacientes que presentan fibrilación auricular.

Para resolver este problema técnico la solicitud en estudio proporciona el uso de Dronedarona o una de sus sales farmacéuticamente aceptables para la preparación de un medicamento para uso en la prevención de la cardioversión en pacientes con historial de fibrilación auricular o aleteo auricular.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A 61 K 031/343.

4. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de las reivindicaciones 1 - 7 no es patentable, de acuerdo con el Art 14.

5. Análisis de las Oposiciones

Argumentaciones de Synthesis

Argumenta al doctora Eliana Isaura Moreno Bohórquez en calidad de apoderada de la sociedad Synthesis, que la presenta solicitud no cumple con los requisitos de patentabilidad, ya que las reivindicaciones de uso y método de tratamiento no son patentables según la legislación, Decisión 486 de la Comunidad Andina de Naciones, Articulo 14. El documento D1: MXPA03005221 afecta la patentabilidad de la presente solicitud, el documento D1 revela formulaciones farmacéuticas de administración parenteral, caracterizada porque comprende Dronedarona o una de sus sales farmacéuticamente aceptables como principio activo, una solución tampón aceptable capaz de mantener el pH de la composición entre 3 – 5, un derivado hidrosoluble de Y-ciclodextrina fisiológicamente aceptable. La Dronedarona tiene dominio cardiovascular como agente anti arrítmico, por tal razón es útil para suprimir o prevenir las alteraciones del ritmo cardiaco como la fibrilación auricular. D1 refiere a una sal farmacéuticamente de Dronedarona tal como clorhidrato presente en las composiciones reveladas de 0.01% a 4 %, por ejemplo 0.1% a 0.8%. Por lo tanto, la presente solicitud carece de novedad de acuerdo a lo revelado en el documento D1, carece de aplicación industrial ya que algunas clausulas reclaman el método terapéutico y estos no son aplicables industrialmente.

Respuesta del Examinador Técnico

Los documentos presentados por la doctora Eliana Isaura Moreno Bohórquez en calidad de apoderada de la sociedad Synthesis corresponden los documentos D1 MXPA03005221, en donde D1 revela una composición farmacéutica de Dronedarona o una de sus sales farmacéuticamente estables preferiblemente de administración parenteral, empleado como agente anti arrítmico. Sin embargo, la presente solicitud en el capitulo reivindicatorio reclama el uso de Dronedarona en la prevención de la cardioversión eléctrica en pacientes que presentan fibrilación auricular, incluyendo factores de riesgo en los pacientes en que es administrado, lo cual no es materia patentable según los Artículos 14 y 21 de la Decisión 486.

Se aclara al solicitante que a pesar de que la materia reivindicada en las clausulas 1 a 7 no es patentable, en el estado de la técnica se divulgan en los documento D1 y D2, el uso de Dronedarona en el tratamiento de arritmias cardiacas.

Ítem	Documento	Título	Fecha de Publicación*
D1	Dronedarone for prevention of atrial fibrillation: A dose-ranging study	European Heart Journal Aug 2003, Vol. 24, No. 16, August 2003	Agosto/2003
D2	Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter	The New Journal Of Medicine	06/Septiembre/2007
D3	Rationale and design of ATHENA: A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patients with Atrial fibrillation/atrial flutter.	Journal Of Cardiovascular Electrophysiology Jan 2008, Vol. 19, No. 1, January 2008	Enero/2008

D1 http://eurheartj.oxfordjournals.org/content/24/16/1481
Divulga un estudio que revela de la Dronedarona fue desarrollado con un compuesto útil en el tratamiento de arritmias cardiacas, de igual manera de Amiodarona, pero con un perfil de seguridad mejorado respecto a Amiodarona, como efectos adversos relacionados con la tiroides (Fl. 106). La Dronedarona es estructuralmente similar a Amiodarona y presenta características electrofisiológicas in vitro de cuatro clases de acción anti arrítmica (Fl. 104). Adicionalmente da a conocer que Dronedarona tiene actividad en la prevención de fibrilación auricular recurrente en pacientes con antecedentes de fibrilación auricular. El estudio se realizo a pacientes donde se administraron dosis de 800, 1200, 1600 mg de Dronedarona o placebo.

D2 http://www.nejm.org/doi/pdf/10.1056/NEJMoa054686 Da a conocer un estudio realizado a grupos de pacientes en donde fueron administrados 800mg/día de Dronedarona, distribuidos en dos dosis/día, en donde fue revelado el uso de Dronedarona para la prevención de fibrilación auricular recurrente o aleteo, en pacientes con antecedente de fibrilación auricular (Fl. 111 - 112). Los pacientes en este estudio presentaron algunos factores de riesgo como hipertensión, enfermedad coronaria.

D3 http://onlinelibrary.wiley.com/doi/10.1111/j.1540-8167.2007.01016.x/pdf
Da a conocer métodos para disminuir la probabilidad de fibrilación/aleteo ventricular en un paciente que comprende la administración de Dronedarona. Por ejemplo en el ensayo DAFNE, seis meses de seguimiento demostraron que el tratamiento con Dronedarona 800mg, dosis diaria, prolongó significativamente el tiempo de recurrencia de la fibrilación auricular en pacientes con fibrilación auricular persistente. Adicionalmente, el documento D2 da a conocer los ensayos clínicos ATHENEA en donde los pacientes de alto riesgo presentaban historial de paroxística o persistente de fibrilación auricular y fueron tratados con 800 mg/día de Dronedarona y seguimiento de 12 – 30 meses, se incluyeron riesgo adicionales como la edad, paciente mayor, hipertensión, diabetes mellitus, ataque isquémico, embolismo sistémico entre otras.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.

JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 16 OCT. 2012

Elaborado por: Paola Duarte
Revisado por: Consuelo Leguizamón Leguizamón
Aprobado por: José Luis Salazar López

European Heart Journal (2003) 24, 1481–1487

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

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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 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 H-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

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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 (%)	10	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.

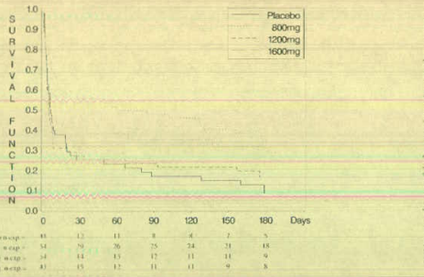

Fig. 1 Kaplan–Meier analysis of the time to first atrial fibrillation relapse according to assigned treatment. The difference in time to atrial fibrillation relapse between the dronedarone 800 mg group and the placebo group was significant (P=0.001). n exp.: number of exposed patients.

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 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<0.0001). 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.

Table 2 Adverse events leading to study drug discontinuation

Adverse event	Placebo n=66 n (%)	800 mg n=76 n (%)	1200 mg n=66 n (%)	1600 mg n=62 n (%)	Dronedarone n=204 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)

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

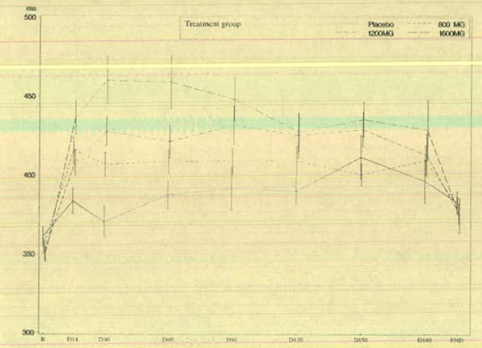

Fig. 2 Plot of QT interval (SEM) over time.

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. Heiss 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, Kuopio 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. Prêtre, Hôpital Sainte Marguerite, Marseille, France; J. Piemontese, 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, Israel; Z. Vered, Cardiology Institute, Zrifin, Israel; 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; FAJE. 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., Dude 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, Oddział 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, Götteborg, Sweden; P. Blomström, Thoracentrum-Akademiska Sjukhuset, Uppsala, Sweden; C. Sylven, Hjärtkliniken, Stockholm, Sweden; S. Juul-Möller, Universitetssjukhuset Mas, Malmö, Sweden; T. Moccetti, Cardiocentro Ticino, Lugano, Switzerland; S. Oswald 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.

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ORIGINAL ARTICLE

Dronedarone for Maintenance of Sinus Rhythm in Atrial Fibrillation or Flutter

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ABSTRACT

BACKGROUND

Amiodarone is effective in maintaining sinus rhythm in atrial fibrillation but is associated with potentially serious toxic effects. Dronedarone is a new antiarrhythmic agent pharmacologically related to amiodarone but developed to reduce the risk of side effects.

METHODS

In two identical multicenter, double-blind, randomized trials, one conducted in Europe (ClinicalTrials.gov number, NCT00259428) and one conducted in the United States, Canada, Australia, South Africa, and Argentina (termed the non-European trial, NCT00259376), we evaluated the efficacy of dronedarone, with 828 patients receiving 400 mg of the drug twice daily and 409 patients receiving placebo. Rhythm was monitored transtelephonically on days 2, 3, and 5; at 3, 5, 7, and 10 months; during recurrence of arrhythmia; and at nine scheduled visits during a 12-month period. The primary end point was the time to the first recurrence of atrial fibrillation or flutter.

RESULTS

In the European trial, the median times to the recurrence of arrhythmia were 41 days in the placebo group and 96 days in the dronedarone group ($P<0.01$). The corresponding durations in the non-European trial were 59 and 158 days ($P<0.002$). At the recurrence of arrhythmia in the European trial, the mean (±SD) ventricular rate was 117.5±29.1 beats per minute in the placebo group and 102.3±24.7 beats per minute in the dronedarone group ($P<0.001$); the corresponding rates in the non-European trial were 116.6±31.9 and 104.6±27.1 beats per minute ($P<0.001$). Rates of pulmonary toxic effects and of thyroid and liver dysfunction were not significantly increased in the dronedarone group.

CONCLUSIONS

Dronedarone was significantly more effective than placebo in maintaining sinus rhythm and in reducing the ventricular rate during recurrence of arrhythmia.

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ATRIAL FIBRILLATION IS THE MOST common arrhythmia requiring hospitalization.[1,2] Although arrhythmia-related symptoms and thromboembolic strokes are significantly reduced by anticoagulation therapy and rate control, sinus rhythm is often associated with improvement in exercise capacity and quality of life.[3] Therefore, restoration and maintenance of sinus rhythm remain major therapeutic goals for patients with atrial fibrillation.[4-6]

Amiodarone is an especially potent atrial antifibrillatory agent,[7] but it induces potentially serious side effects in some patients.[7,8] Thus, compounds that are devoid of such effects but that retain the antiarrhythmic potential of amiodarone are therapeutically desirable.[7,9] Dronedarone is a benzofuran derivative with an electropharmacologic profile closely resembling that of amiodarone[9,10] but with structural differences intended to eliminate the effects of amiodarone on thyroid and pulmonary functions.[9,10] In addition, the elimination half-life of dronedarone is 1 to 2 days, as compared with 30 to 55 days for amiodarone.[10] We investigated the hypothesis that dronedarone is superior to placebo for maintaining sinus rhythm after electrical, pharmacologic, or spontaneous conversion from atrial fibrillation or atrial flutter.

METHODS

STUDY DESIGN

The European Trial in Atrial Fibrillation or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm (EURIDIS, NCT00259428) and the American–Australian–African Trial with Dronedarone in Atrial Fibrillation or Flutter Patients for the Maintenance of Sinus Rhythm (ADONIS, NCT00259376) were two identical, placebo-controlled, multicenter, double-blind, parallel-group trials sponsored by Sanofi-Aventis. The European trial was conducted in 12 European countries, and the non-European trial was conducted in the United States, Canada, Australia, South Africa, and Argentina.

The study protocols were approved by the human-research review boards at each participating institution. A single common steering committee designed the studies and the data analysis plans in collaboration with the sponsor. An independent data and safety monitoring board oversaw the safety of patients. All data-management activities were the responsibility of the sponsor. Data entry, verification, and validation were performed with the use of standard computer software (Clintrial 4.3), and data were stored in an Oracle database on a Sun Solaris computer. At study termination, the database was locked and transferred to the biostatistics department at Sanofi-Aventis for analysis. The academic investigators had independent access to the raw data. Dr. Singh, who wrote the manuscript with input from the other steering-committee members and from Sanofi-Aventis personnel, vouches for the accuracy and completeness of the data and the analysis.

PATIENTS

Patients qualifying for enrollment were of either sex and at least 21 years of age, had had at least one episode of atrial fibrillation (as seen on electrocardiography) in the preceding 3 months, and were in sinus rhythm for at least 1 hour before randomization. Excluded from the study were patients with permanent atrial fibrillation (i.e., a duration of at least 12 months); women who could become pregnant and who were not using birth control; patients who had had torsades de pointes; patients with persistent bradycardia of less than 50 beats per minute, a PR interval of 0.28 second or more on electrocardiography, second-degree (or higher) atrioventricular block, and clinically significant sinus-node disease without an implanted pacemaker; patients who were taking class I or III antiarrhythmic agents; patients with New York Heart Association class III or IV congestive heart failure; and patients with a serum creatinine level of 1.7 mg per deciliter (150 μmol per liter) or more, severe electrolyte abnormalities, and clinically significant hepatic, pulmonary, endocrine, or other disorders associated with atrial fibrillation. Previous treatment with amiodarone was permitted, and patients who had received the drug could be enrolled immediately after its discontinuation. Written informed consent was obtained from all patients.

BASELINE EVALUATION, RANDOMIZATION, AND THERAPY

All study patients underwent a baseline evaluation that included a medical history, symptom review, cardiovascular examination, assessment of vital signs, 12-lead electrocardiography, chest radiog-

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raphy, and laboratory tests, including a complete blood count and tests of serum electrolytes, urea, creatinine, and cholesterol and thyroid and liver function. Left atrial size and left ventricular ejection fraction were determined by two-dimensional echocardiography. Eligible patients who were not in sinus rhythm during screening could be enrolled if they underwent successful cardioversion and remained in sinus rhythm for at least 1 hour.

After a 7-day screening period, eligible patients were randomly assigned in a 2:1 ratio to receive either 400 mg of oral dronedarone twice daily or a matching placebo. A stochastic randomization procedure suggested by Pocock and Simon[31] and revised by Freedman and White[32] was used. On the first day of the study, symptoms were evaluated, vital signs were assessed, the assigned study drug was administered, and 12-lead electrocardiography was performed.

FOLLOW-UP

We scheduled follow-up visits that included a review of symptoms, assessment of vital signs, and performance of electrocardiography on days 7, 14, and 21 and at 2, 4, 6, 9, and 12 months. The above-mentioned blood tests were repeated on day 21 and at months 4, 9, and 12. Chest radiography was repeated in the case of pulmonary symptoms.

All enrolled patients were given a transtelephonic electrocardiographic monitor and were instructed in its use. Patients transmitted electrocardiograms on days 2, 3, and 5; at months 3, 5, 7, and 10; and whenever they had symptoms. On each occasion, two electrocardiograms were recorded approximately 10 minutes apart and were evaluated at a central core laboratory (MDS Pharma Services, Paris) by investigators who were unaware of study-group assignments to confirm the recurrence of atrial fibrillation. Each time an electrocardiogram was recorded, the patient was contacted to confirm the occurrence of one or more of the following symptoms: palpitations, dizziness, fatigue, chest pain, and dyspnea. Reported symptoms were taken into account if they were accompanied by atrial fibrillation. If oral anticoagulation therapy was administered, the international normalized ratio was monitored locally.

STUDY END POINTS

The primary end point was the time from randomization to the first documented recurrence of atrial fibrillation, defined as an episode lasting for at least 10 minutes and confirmed by two consecutive recordings taken 10 minutes apart on 12-lead electrocardiography or transtelephonic monitoring. The main secondary end points were symptoms related to atrial fibrillation during recordings of 12-lead electrocardiography or transtelephonic monitoring and the mean ventricular rate during the first recurrence.

STATISTICAL ANALYSIS

The hypothesis for determining the number of patients needed for the study was derived from data from efficacy trials of antiarrhythmic drugs for the treatment of atrial fibrillation.[33-35] It was presumed that 60% of patients in the placebo group would have a recurrence of arrhythmia within 12 months; a relative decrease in this rate of at least 25% was expected in the dronedarone group (i.e., a 45% recurrence rate).

With a sample size of 552 patients (368 in the dronedarone group and 184 in the placebo group), each trial would have a power of 90% to detect a between-group difference, assuming a 20% dropout rate and a 1-year follow-up period. The primary analysis was performed according to a modified intention-to-treat principle, with all randomized patients who received at least one dose of a study drug included. A secondary on-treatment analysis was also performed. A two-sided Fisher's exact test was used for qualitative measures. The event-free probability curves were estimated by the nonparametric Kaplan–Meier technique, with 95% confidence intervals. A standard log-rank technique was used to test the null hypothesis of identical Kaplan–Meier curves in the two study groups. All reported P values are two-sided, and P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

PATIENTS

In the European trial, 680 patients were screened, and 612 were randomly assigned to study groups to receive treatment (411 to the dronedarone group and 201 to the placebo group). In the non-European trial, 731 patients were screened, and 625 were randomly assigned to receive treatment (417 to the dronedarone group and 208 to the placebo group). Three patients in the European trial and four in the non-European trial did not receive a study drug (Fig. 1).

Table 1 presents the baseline characteristics of the patients in the European and non-European trials, individually and combined. The mean age of all patients was 63 years, and 67% were men; 41% had structural heart disease. There were 60 patients (10%) with atrial flutter in the European trial and 71 (11%) in the non-European trial. In the European trial, 67 patients in the dronedarone group and 25 in the placebo group discontinued the study prematurely; in the non-European trial, the corresponding numbers were 81 and 36.

PRIMARY END POINT

In the European trial, according to the modified intention-to-treat analysis, the median times from randomization to a documented recurrence of atrial fibrillation were 96 days in the dronedarone group and 41 days in the placebo group. At 12 months, 67.1% of patients in the dronedarone group and 77.5% of patients in the placebo group had had a recurrence of atrial fibrillation (hazard ratio for the dronedarone group, 0.78; 95% confidence interval [CI], 0.64 to 0.96; P=0.01) (Table 2). On-treatment analysis of the same population had similar results (P=0.01).

In the non-European trial, according to a modified intention-to-treat analysis, the median times from randomization to a documented recurrence of atrial fibrillation were 158 days in the dronedarone group and 59 days in the placebo group. At 12 months, 61.1% of patients in the dronedarone group and 72.8% of patients in the placebo group had had a recurrence of atrial fibrillation (hazard ratio, 0.73; 95% CI, 0.59 to 0.89; P=0.002) (Table 2). The results of on-treatment analysis were confirmatory (P=0.002).

For the two trials combined, the median times to a documented recurrence of atrial fibrillation were 116 days in the dronedarone group and 53 days in the placebo group. At 12 months, the rates of recurrence were 64.1% in the dronedarone group and 75.2% in the placebo group (hazard ratio, 0.7%; 95% CI, 0.65 to 0.87; P<0.001) (Table 2). Figure 2 shows the Kaplan–Meier cumulative incidence curves for the adjudicated first recurrence in patients in the European trial and the non-European trial, separately and combined. The association of dronedarone with a reduction in the risk of recurrence of atrial fibrillation, as compared with placebo, was consistent for a series of clinically important subgroups (Fig. 3).

A separate preplanned analysis excluded patients with a study-drug exposure of less than 5 days before the occurrence of the primary end point (either because the patient discontinued treatment within 5 days or because atrial fibrillation recurred within 5 days). In the European trial, this analysis showed that patients in the dronedarone group had a reduction in the risk of adjudicated recurrence of 29% from day 5 to 12 months after randomization, as compared with those in the placebo group (P=0.006 by the log-rank test). In the non-European trial, the reduction was 26% (P=0.02 by the log-rank test) (Table 2).

HEART RATE AND QT INTERVAL IN SINUS RHYTHM

In the combined European and non-European trials, the effects of dronedarone, as compared with those of placebo, on the mean heart rate, QT interval, and QT interval corrected for heart rate (QTc) were investigated in preplanned analyses (see the Supplementary Appendix, available with the full text of this article at www.nejm.org). As compared with baseline values, in the dronedarone group, heart rate was reduced by 6.8%, the QT interval was prolonged by 23.4 msec, and the QTc interval was prolonged by 9.0 msec (P<0.001 for all comparisons with the placebo group), without significant effects on the QRS duration.

VENTRICULAR RATE AT FIRST RECURRENCE

In both trials, ventricular rates during the recurrence of atrial fibrillation were evaluated in preplanned analyses. In the European trial, the mean (±SD) ventricular rate during the first adjudicated recurrence was 102.3±24.7 beats per minute in the dronedarone group and 117.5±29.1 beats per minute in the placebo group (P<0.001). The corresponding numbers for the non-European trial were 104.6±27.1 beats per minute in the dronedarone group and 116.6±31.9 beats per minute in the placebo group (P<0.001) (Table 2).

SYMPTOMATIC FIRST RECURRENCE

In another preplanned analysis, the rates of symptomatic recurrence of atrial fibrillation were compared between the study groups in each trial. The majority of documented first recurrences were symptomatic, and the pattern of symptoms did not differ between the dronedarone group and the pla-

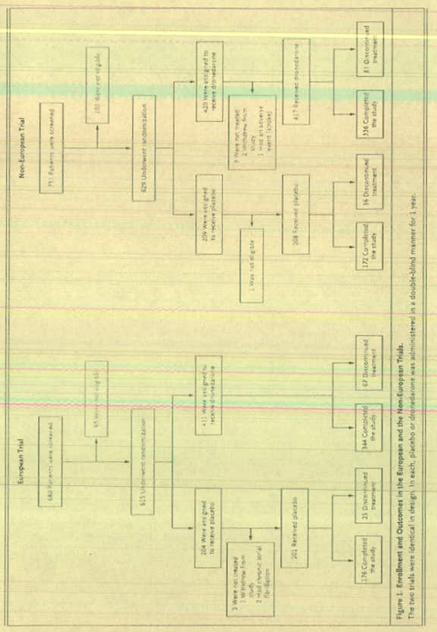

Figure 1. Enrollment and Outcomes in the European and the Non-European Trials.
The two trials were identical in design. In each, placebo or dronedarone was administered in a double-blind manner for 1 year.

Table 1. **Baseline Characteristics of the Study Patients.***

Characteristic	European Trial		Non-European Trial		Combined Trials	
	Placebo (N = 204)	Dronedarone (N = 411)	Placebo (N = 208)	Dronedarone (N = 417)	Placebo (N = 809)	Dronedarone (N = 828)
Sex — no. (%)						
Female	61 (30.3)	126 (30.7)	68 (32.7)	124 (29.7)	129 (31.5)	250 (30.2)
Male	140 (69.7)	285 (69.3)	140 (67.3)	293 (70.3)	280 (68.5)	578 (69.8)
Age — yr	61.3±10.7	62.3±10	63±11.4	64.6±11.3	62.2±11.1	63.5±10.7
Race — no. (%)†						
White	201 (100)	409 (99.5)	199 (95.7)	391 (93.8)	400 (97.8)	800 (96.6)
Black	0	0	3 (1.4)	9 (2.2)	3 (0.7)	9 (1.1)
Asian	0	2 (0.5)	0	4 (1.0)	0	6 (0.7)
Other	0	0	6 (2.9)	13 (3.1)	6 (1.5)	13 (1.6)
Body-mass index — no. (%)‡						
<30	143 (73.3)	287 (70.9)	130 (63.7)	251 (61.2)	273 (68.4)	538 (66.0)
≥30	52 (26.7)	118 (29.1)	74 (36.3)	159 (38.8)	126 (31.6)	277 (34.0)
Weight — kg	86.43±14.78	83.84±14.39	87.83±19.27	88.61±19.88	87.14±17.22	86.25±17.53
Cardiovascular history — no. (%)						
Structural heart disease§	65 (33.3)	149 (36.1)	94 (45.6)	199 (48.5)	159 (39.7)	348 (42.4)
Hypertension	108 (53.7)	255 (62.0)	97 (46.6)	242 (58.0)	205 (50.1)	497 (60.0)
Coronary artery disease¶	31 (15.4)	91 (22.1)	44 (21.2)	104 (24.9)	75 (18.1)	195 (23.6)
Cardiac valvular disease	19 (9.5)	50 (12.2)	42 (20.2)	86 (20.6)	61 (14.9)	136 (16.4)
Nonischemic cardiomyopathy	11 (5.5)	16 (3.9)	19 (9.1)	34 (8.2)	30 (7.3)	50 (6.0)
Implanted pacemaker	7 (3.5)	33 (8.0)	13 (6.2)	31 (7.4)	20 (4.9)	64 (7.7)
Implanted cardioverter-defibrillator	3 (1.5)	0	2 (1.0)	6 (1.4)	5 (1.2)	6 (0.7)
Rheumatic heart disease	6 (3.0)	7 (1.7)	8 (3.8)	18 (4.3)	14 (3.4)	25 (3.0)
Hypertrophic cardiomyopathy	8 (4.0)	10 (2.4)	4 (1.9)	13 (3.1)	12 (2.9)	23 (2.8)
Congenital heart disease	2 (1.0)	9 (2.2)	1 (0.5)	4 (1.0)	3 (0.7)	13 (1.6)
Left ventricular ejection fraction — %	59.83±9.37	59.57±10.25	57.21±12.24	57.91±11.23	58.5±10.98	58.75±10.77
Left atrial anteroposterior diameter — mm	42.7±6.7	42.4±6.6	42.0±6.9	42.9±7.4	42.4±6.8	42.6±7.0
Congestive heart failure — no. (%)‖						
Any disease	37 (18.4)	65 (15.8)	36 (17.3)	78 (18.7)	73 (17.8)	143 (17.3)
NYHA class I	16 (8.0)	19 (4.6)	10 (4.8)	28 (6.7)	26 (6.4)	47 (5.7)
NYHA class II	21 (10.4)	46 (11.2)	26 (12.5)	50 (12.0)	47 (11.5)	96 (11.6)
Symptoms of atrial fibrillation in the 3 months before randomization — no. (%)	175 (87.1)	352 (85.6)	180 (86.5)	374 (89.7)	355 (86.8)	726 (87.7)
Recent cardioversion (within 5 days before randomization) — no. (%)	75 (37.3)	153 (37.2)	46 (22.1)	90 (21.6)	121 (29.6)	243 (29.3)

cebo group. In the European trial, 37.1% of patients in the dronedarone group and 47.5% of those in the placebo group had symptomatic recurrences ($P=0.006$ by the log-rank test). In the non-European trial, symptomatic recurrences occurred in 38.3% of patients in the dronedarone group and 44.5% of those in the placebo group ($P=0.02$ by the log-rank test). The corresponding numbers for the pooled data were 37.7% and 46.0% ($P<0.001$ by the log-rank test) (Table 2). The Prentice cumu-

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Table 1. (Continued.)

Characteristic	European Trial		Non-European Trial		Combined Trials	
	Placebo (N = 201)	Dronedarone (N = 411)	Placebo (N = 208)	Dronedarone (N = 417)	Placebo (N = 409)	Dronedarone (N = 828)
Concomitant cardiovascular therapy — no. (%)						
Digoxin	42 (20.9)	51 (12.4)	53 (25.5)	94 (22.5)	95 (23.2)	145 (17.5)
Calcium-channel blocker (rate-lowering)	23 (11.4)	76 (18.5)	55 (26.4)	103 (24.7)	78 (19.1)	139 (16.8)
Beta-blocker (except sotalol)	124 (61.7)	245 (59.6)	114 (54.8)	208 (49.9)	238 (58.2)	453 (54.7)
Oral anticoagulant	142 (70.6)	271 (66.4)	149 (71.6)	298 (71.5)	291 (71.1)	571 (69.0)
Long-term antiplatelet therapy	64 (31.8)	135 (32.8)	88 (42.3)	191 (45.8)	152 (37.2)	326 (39.4)
Statin	52 (25.9)	95 (23.1)	79 (38.0)	168 (40.3)	131 (32.0)	263 (31.8)
ACE inhibitor	79 (39.3)	176 (42.8)	80 (38.5)	151 (36.2)	159 (38.9)	327 (39.5)
Previous antiarrhythmic treatment — no. (%)						
Class IA	19 (9.5)	39 (9.5)	21 (10.1)	43 (10.3)	40 (9.8)	82 (9.9)
Class IB	0	3 (0.7)	0	3 (0.7)	0	6 (0.7)
Class IC	69 (34.3)	120 (29.2)	39 (18.8)	70 (16.8)	108 (26.4)	190 (22.9)
Class II	61 (30.3)	117 (28.5)	6 (2.9)	22 (5.3)	67 (16.4)	139 (16.8)
Class III	8 (4.0)	31 (7.5)	19 (9.1)	55 (13.2)	27 (6.6)	86 (10.4)
Class IV	22 (10.9)	43 (10.5)	16 (7.7)	29 (7.0)	38 (9.3)	72 (8.7)
Amiodarone	56 (27.9)	101 (24.6)	70 (33.7)	142 (34.1)	126 (30.8)	243 (29.3)
Sotalol	59 (29.4)	119 (31.4)	53 (25.5)	85 (20.4)	112 (27.4)	214 (25.8)

* Plus–minus values are means ±SD. NYHA denotes New York Heart Association, and ACE angiotensin-converting enzyme.

† Race was determined by the investigators on the basis of hospital records.

‡ The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters. In the European trial, data were missing for six subjects in the placebo group and six in the dronedarone group; in the non-European trial, data were missing for four subjects in the placebo group and seven in the dronedarone group.

§ In the European trial, data were missing for six subjects in the placebo group and one in the dronedarone group; in the non-European trial, data were missing for two subjects in the placebo group and seven in the dronedarone group.

¶ The diagnosis of coronary artery disease was made on the basis of the clinical history and the results of investigational tests.

‖ The diagnosis of congestive heart failure (NYHA class I and II) was made on clinical grounds. Patients who were classified as having NYHA class I congestive heart failure had received a diagnosis of the disease but had no symptoms.

lative incidence curves[16] for a symptomatic first recurrence for the pooled data are shown in the Supplementary Appendix.

HOSPITALIZATION OR DEATH

In the European Trial, a post hoc analysis revealed that 21.2% of patients in the dronedarone group had been hospitalized or had died at 12 months, as compared with 32.0% of those in the placebo group (hazard ratio, 0.66; 95% CI, 0.47 to 0.93; P = 0.02). In the non-European trial, 24.5% of patients in the dronedarone group had been hospitalized or had died, as compared with 29.8% of those in the placebo group (hazard ratio, 0.80; 95% CI, 0.56 to 1.14; P=0.22). The corresponding numbers in the combined analysis were 22.8% and 30.9% (hazard ratio, 0.73; 95% CI, 0.57 to 0.93; P=0.01) (Table 2).

ADVERSE EVENTS

Table 3 shows the incidence of selected adverse events in the two study groups. Most of these specific adverse events are shown because they include many of the known side effects of amiodarone. In addition, there was a higher incidence of elevated serum creatinine levels in the dronedarone group than in the placebo group (2.4% vs. 0.2%, P=0.004).

In addition to the events listed in Table 3, one patient in the dronedarone group received the diagnosis of interstitial lung disease, which was reported after the patient had completed the 1-year

Table 2. Study End Points.*

Variable	European Trial			Non-European Trial			Combined Trials		
	Placebo	Dronedarone	Hazard Ratio (95% CI)	Placebo	Dronedarone	Hazard Ratio (95% CI)	Placebo	Dronedarone	Hazard Ratio (95% CI)
Time to first recurrence of atrial fibrillation									
No. of patients	201	411		208	417		409	828	
Median (days)	41	96		59	155		93	116	
Recurrence rate at 12 mo (%)	77.5	67.1	0.78 (0.64–0.94)	72.8	63.1	0.73 (0.59–0.89)	75.2	64.3	0.75 (0.65–0.87)
Recurrence rate at treatment end (%)	76.5	61.5	0.73 (0.60–0.90)	72.7	58.8	0.71 (0.57–0.88)	74.7	62.3	0.74 (0.64–0.86)
Recurrence at 12 mo									
No. of patients	148	307		145	327		294	634	
Analysis excluding drug discontinuation (%)	69.5	56.4	0.75 (0.59–0.95)	62.6	51.3	0.74 (0.57–0.96)	66.2	53.8	0.72 (0.60–0.86)
Persistent or permanent atrial fibrillation	47.5	31.1	0.57 (0.44–0.74)	64.3	38.1	0.54 (0.42–0.70)	44.0	31.7	0.52 (0.44–0.62)
Ventricular rate at first recurrence (beats/min)									
No. of patients	137	199		102	148		219	387	
Mean rate (bpm)	117.5±28.3	103.3±24.7		116.6±31.9	104.6±27.1		117.1±30.4	103.4±25.9	
Hospitalization or death (%)	32.0	21.2	0.66 (0.47–0.93)	29.8	24.5	0.80 (0.56–1.14)	30.9	22.8	0.73 (0.57–0.93)

* Plus–minus values are means ±SD. TTVF denotes transtelephonic monitoring.

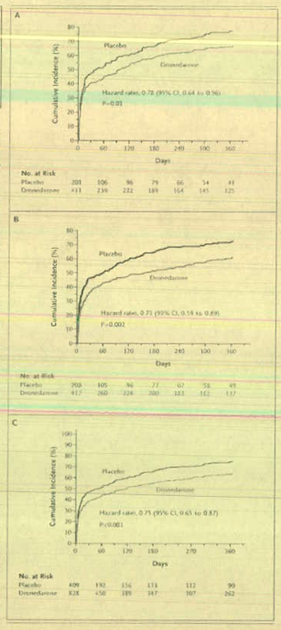

Figure 2. **Kaplan–Meier Cumulative Incidence of the Adjudicated First Recurrence of Atrial Fibrillation or Flutter.**

The times to recurrence of atrial fibrillation or flutter are shown for the European trial (Panel A), the non-European trial (Panel B), and the two trials combined (Panel C). The hazard ratios were determined for the dronedarone group as compared with the placebo group. CI denotes confidence interval.

follow-up. This patient also had mitral-valve disease and a history of congestive heart failure and had had a viral infection during the week preceding the report of the diagnosis. The pulmonary findings subsequently resolved without sequelae. A second patient in the dronedarone group was reported to have pulmonary fibrosis, which on further investigation and blinded radiologic review had been present on chest radiography at baseline. Ventricular arrhythmias occurred infrequently in both study groups; no episodes of torsades de pointes were reported.

DISCUSSION

The European trial and the non-European trial were large, double-blind, placebo-controlled trials, each comparing the efficacy of dronedarone with that of placebo for the maintenance of sinus rhythm in patients with atrial fibrillation. We found that dronedarone reduced the incidence of a first recurrence, as well as a symptomatic first recurrence, within 12 months after randomization. Dronedarone also significantly reduced the ventricular rate during the recurrence of arrhythmia. In addition, in a post hoc analysis, dronedarone significantly reduced the rate of hospitalization or death.

In both the European and non-European trials, dronedarone prolonged the time to the recurrence of atrial fibrillation by a factor of more than 2, as compared with placebo. This finding is consistent with the drug's propensity for markedly prolonging the atrial effective refractory period[16,17] by inducing multiple ion-channel blockade.[13] However, the effectiveness of dronedarone in maintaining sinus rhythm in atrial fibrillation cannot be reliably compared with that of amiodarone or sotalol on the basis of these data. The latter agents have been evaluated in studies that may have differed markedly from our trials with respect to the trial design, study population, and pattern of atrial fibrillation (paroxysmal or persistent).[3,26,28,29] In our trials, patients were in sinus rhythm at the time of randomization, but the trial design did not permit a clear distinction between patients who had persistent atrial fibrillation and those with paroxysmal atrial fibrillation. It is likely that most of the patients in our trials who did not require direct-current cardioversion during the 5 days preceding randomization (71%) had paroxysmal atrial fibrillation or flutter. The results of the subgroup analyses underscore the consistent effectiveness of dronedarone in maintaining sinus rhythm in patients with atrial fibrillation encompassing a wide range of covariates.

In our trials, the effectiveness of 400 mg of dronedarone twice daily in maintaining sinus rhythm without major prolongation of either the QT or the QTc interval suggests a measure of atrial selectivity of the drug action, as reported in studies involving rabbit ventricular and atrial cells.[17,18] Amiodarone and dronedarone both limit the risk of torsades de pointes by attenuating after-depolarization activity in the M cell and Purkinje fiber activity[30-34] in the ventricular myocardium. In the case of amiodarone, torsades de pointes is rare,[2,35] and to date an unequivocal case of torsades induced by dronedarone has not been noted despite the lengthening of the QT and QTc intervals by 25 and 9 msec, respectively, in our combined trials.

In neither of the trials did we directly compare dronedarone with amiodarone. Therefore, we cannot be certain that the efficacy of dronedarone is similar to that of amiodarone, nor can we state with certainty that the rate of adverse events is significantly lower. On the basis of experience with amiodarone in other trials, our findings suggest these conclusions, but a definitive answer will require a trial that directly compares the two drugs. Furthermore, the low rate of adverse events (especially pulmonary toxic effects) may be explained in part by the relatively short duration of our trials and by the fact that chest radiography and assessment of pulmonary function were not performed unless symptoms were present.

Subgroup	No. of Patients	Hazard Ratio for Event (95% CI)	Hazard Ratio	P Value for Interaction
Structural heart disease				0.59
Yes	664	0.72 (0.61–0.85)		
No	714	0.74 (0.62–0.89)		
Hypertension				0.62
Yes	702	0.73 (0.60–0.89)		
No	535	0.79 (0.64–0.97)		
Left atrial diameter				0.10
<40 mm	463	0.65 (0.51–0.82)		
≥40 mm	735	0.83 (0.69–0.99)		
Heart failure criteria met				0.10
Yes	216	0.59 (0.42–0.83)		
No	944	0.81 (0.69–0.95)		
Conversion to sinus rhythm in ≤5 days				0.37
Yes	364	0.76 (0.59–0.97)		
No	879	0.74 (0.64–0.90)		
Previous use of amiodarone				0.21
Yes (stopped for trial)	223	0.60 (0.43–0.84)		
No	1041	0.79 (0.67–0.92)		
Previous use of antiarrhythmic drugs				0.11
Yes (stopped for trial)	903	0.70 (0.59–0.82)		
No	334	0.92 (0.68–1.25)		

Figure 3. **Hazard Ratio for the Adjudicated First Recurrence of Atrial Fibrillation or Flutter, According to Selected Baseline Characteristics.**

The scale for the hazard ratios, which were determined from Cox models comparing the dronedarone group with the placebo group, is logarithmic. Dronedarone had a variable but consistently favorable effect, as compared with placebo, in reducing the first recurrence of atrial fibrillation or flutter.

Table 3. Selected Adverse Events and Laboratory Abnormalities.*

Event	Treatment Group		P Value†
	Dronedarone (N=828)	Placebo (N=409)	
Death — no. (%)			
Any cause	8 (1.0)	3 (0.7)	1.00
Sudden death	4 (0.5)	1 (0.2)	1.00
Stroke — no. (%)‡	4 (0.5)	3 (0.7)	0.69
Pulmonary event — no. (%)§			
Cough	19 (2.3)	7 (1.7)	0.67
Dyspnea	27 (3.3)	15 (3.7)	0.74
Endocrine event — no./total no. (%)¶			
Hyperthyroidism	67/801 (8.4)	56/396 (14.1)	0.002
Hypothyroidism	44/801 (5.5)	14/396 (3.5)	0.15
Cardiac event — no. (%)			
Bradycardia or conduction block‖			
Any event	22 (2.7)	8 (2.0)	0.56
Serious event	8 (1.0)	3 (0.7)	1.00
Heart failure or shock**			
Any event	20 (2.4)	4 (1.0)	0.12
Serious event	13 (1.6)	3 (0.7)	0.29
Ventricular arrhythmia††	6 (0.7)	2 (0.5)	1.00
Neurologic event — no. (%)			
Insomnia or other sleep disorder	12 (1.4)	6 (1.5)	1.00
Memory impairment	1 (0.1)	0	1.00
Peripheral neuropathy	0	1 (0.2)	0.33
Paresthesia	11 (1.3)	4 (1.0)	0.78
Tremor	6 (0.7)	2 (0.5)	1.00
Gastrointestinal or hepatic event			
Diarrhea — no. (%)	59 (7.1)	20 (4.9)	0.14
Nausea — no. (%)	36 (4.3)	14 (3.4)	0.54
Abnormality of liver function — no./total no. (%)‡‡	100/822 (12.2)	55/405 (13.6)	0.52
Dermatologic event — no. (%)			
Photosensitivity or skin discoloration§§	6 (0.7)	1 (0.2)	0.44
Other			
Elevation of serum creatinine — no. (%)	20 (2.4)	1 (0.2)	0.004

* Adverse events were defined as those occurring between the first administration of a study drug and the last administration plus 10 days.

† P values were calculated with the use of Fisher's exact test.

‡ Stroke includes cerebral artery embolism, cerebrovascular accident, cerebral infarction, and transient ischemic attack.

§ Dyspnea includes exacerbated, exertional, and nocturnal dyspnea.

¶ Hyperthyroidism was defined as a free triiodothyronine or free thyroxine level above the normal range or a thyrotropin level below the normal range. Hypothyroidism was defined as a free triiodothyronine or free thyroxine level below the normal range or a thyrotropin level above the normal range. Patients with inconsistent changes in these measures were excluded from the analysis.

‖ Bradycardia or conduction block includes complete atrioventricular block. Serious adverse events include complete atrioventricular block, sinus bradycardia, first-degree atrioventricular block, and nodal arrhythmia.

** Heart failure or shock includes congestive cardiac failure, cardiac failure, left ventricular failure, and right ventricular failure. Serious adverse events include congestive cardiac failure, cardiac failure, left ventricular failure, cardiogenic shock, and ventricular dysfunction.

†† Ventricular arrhythmia includes ventricular tachycardia, ventricular extrasystoles, and ventricular fibrillation.

‡‡ An abnormality of liver function was defined as a level of alanine aminotransferase or aspartate aminotransferase of more than 2 times the upper limit of the normal range, an alkaline phosphatase level of more than 1.5 times the upper limit of the normal range, a γ-glutamyltransferase level of 3 times the upper limit of the normal range or more, or a total bilirubin level of 2 mg per deciliter (34 μmol per liter) or more. Patients with no abnormality and with at least one missing measurement of liver function were excluded.

§§ Photosensitivity or skin discoloration includes photosensitive rash and photosensitivity reaction.

As in many other trials examining the efficacy of treatments for atrial fibrillation, it is likely that we were not able to detect every episode of recurrent arrhythmia in our study patients. Follow-up electrocardiograms were obtained at frequent intervals and in the case of symptoms. The fact that the majority of first documented recurrences were symptomatic strongly suggests that not all episodes were detected, since the majority of episodes of atrial fibrillation in the general population may be asymptomatic. Continuous monitoring of all study patients over the long term was beyond the scope of these trials and typically has not been considered essential for the interpretation of such studies.

A previous study, the Antiarrhythmic Trial with Dronedarone in Moderate to Severe Congestive Heart Failure Evaluating Morbidity Decrease (ANDROMEDA), was discontinued early because an interim safety analysis suggested a potential increase in the risk of death with dronedarone therapy. The discontinued trial involved patients with moderate-to-severe congestive heart failure and ventricular dysfunction, and thus investigated a different (and higher-risk) population than the patients we studied. In our trials, the rates of death from any cause and sudden death in the dronedarone group did not differ significantly from those in the placebo group. Nonetheless, the experience with the ANDROMEDA trial indicates that dronedarone may be associated with an increased risk of death in patients with advanced congestive heart failure and that the drug should not be used in such patients until appropriate data are gathered.

In conclusion, our trials showed that the rates of the first recurrence of atrial fibrillation and of the first symptomatic recurrence at 1 year were significantly reduced with dronedarone, as compared with placebo. Dronedarone also reduced the ventricular rate in atrial fibrillation during recurrences of arrhythmia. The available data are not directive with respect to the rates of adverse effects, as compared with those of amiodarone.

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APPENDIX

The following authors and other investigators participated in the European trial and the non-European trial: **Steering Committee:** B.N. Singh (chair), E. Aliot, A. Capucci, S.J. Connolly, H.J.G.M. Crijns, S. Hohnloser, P. Kowey, L.D. Roy, and D. Radzik. **Data and Safety Monitoring Board:** *Dijon, France* — A. Leizorovicz (chair); *London* — J. Camm; *Miami* — R. Myerburg.

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Rationale and Design of ATHENA: A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg Bid for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in PatiENts with Atrial Fibrillation/Atrial Flutter

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Rationale and Design of ATHENA. *Background:* **Atrial fibrillation (AF) is the most commonly encountered clinical arrhythmia, predominantly affecting elderly patients. There is a continued need for new antiarrhythmic drugs to treat the ever-increasing number of patients with this arrhythmia. Dronedarone is a new antiarrhythmic compound currently being developed for treatment of AF.**

Methods: **The ATHENA trial (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter) is the largest single antiarrhythmic drug trial ever conducted. More than 4,600 patients with a history of AF or atrial flutter (AFL) have been randomized to receive dronedarone 400 mg bid or matching placebo. The primary study endpoint is time to first cardiovascular hospitalization or death from any cause. The study has completed patient enrollment in December 2006 and is expected to end follow-up 1 year later.**

Conclusion: **ATHENA will be the largest efficacy and safety trial of dronedarone, a multichannel blocker compound with properties from class I, II, III, and IV antiarrhythmic drugs developed to treat patients with AF.** *(J Cardiovasc Electrophysiol, Vol. 19, pp. 69-73, January 2008.)*

atrial fibrillation, antiarrhythmic drugs, mortality, cardiovascular hospitalization, dronedarone

Introduction

In the face of a burgeoning older population, the prevalence of atrial fibrillation (AF) is rapidly increasing.[1] AF is associated with increased morbidity and mortality,[2,3] particularly in patients with structural heart disease (impairing systolic or diastolic[4] LV function. In Western societies, AF has grown as a major contributing cause of hospitalization and thus, socioeconomic, burden.[5] Accordingly, attempts to restore and maintain sinus rhythm (SR) in patients with AF are currently the preferred treatment modalities in most institutions, despite the results of studies showing similar mortality figures for patients undergoing rhythm or rate control.[6–8] Given the epidemic character of the rhythm disorder, non-pharmacological therapy (particularly catheter ablation) is only feasible in selected patient populations, such as younger patients with symptomatic AF but no or only minor structural heart disease. For the great majority of elderly or old patients in whom more or less advanced heart disease constitutes the background of the arrhythmia, pharmacological treatment will remain the mainstay of therapy.

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Antiarrhythmic Drug Therapy in AF

A variety of antiarrhythmic drugs is currently used to treat patients with AF, mostly to prevent recurrent AF after successful restoration of SR. As recently demonstrated in a comprehensive meta-analysis, class IA, IC, and III drugs are effective in maintaining SR, but increase adverse effects.[9] Moreover, at least for the class IA and pure class III (SWORD trial) drugs, it was shown that they increase mortality. This is in agreement with findings of the AFFIRM trial, in which the only predictor of improved outcome was maintenance of SR, but on the other hand, the use of contemporary antiarrhythmic drugs was found to be associated with adverse prognostic implications.[10] Accordingly, there is a continued need for more effective, safer, and well-tolerated antiarrhythmic drugs for therapy of millions of patients who are not primarily candidates for nonpharmacological therapy of AF.

Development of Dronedarone

Dronedarone is a noniodinated benzofuran derivative with a sulfonamide group on the benzofuran ring. The electrophysiological properties of dronedarone are very similar to those of amiodarone, which is at present the most effective drug to maintain SR in patients with AF. Like amiodarone, dronedarone demonstrates electrophysiological characteristics belonging to all four Vaughan-Williams classes: it blocks sodium channels, shows a noncompetitive antiadrenergic activity, prolongs action potential and refractory periods, and has calcium antagonist properties. Dronedarone is effective in experimental models of AF, ventricular tachycardia, and ventricular fibrillation.[11–14]

The first clinical study to evaluate the efficacy and safety of dronedarone in maintaining SR in patients with a history of AF was the dose-ranging Dronedarone Atrial FibrillatioN Study after Electrical Cardioversion (DAFNE) trial.[15] In DAFNE, patients with persistent AF were randomly assigned to treatment with dronedarone 400 mg, 600 mg, and 800 mg bid or placebo. Analyses were carried out on 199 of 270 patients who entered the maintenance phase following pharmacological conversion or, where unsuccessful, DC conversion, with time to first recurrence as the primary study endpoint. Six-month follow-up showed that treatment with dronedarone 400 mg bid significantly prolonged the time to AF recurrence. The median time to recurrence was 60 days in the dronedarone 400 mg bid, treatment arm compared with 5.3 days in placebo recipients resulting in a relative risk reduction of 55% (95% CI, 28–72%; P = 0.001). Spontaneous conversion to SR occurred in 3.8–14.8% of dronedarone-treated patients compared with only 3.1% on placebo (P = 0.026). During recurrent AF, a significant slowing of the ventricular rate was also observed during DAFNE.

These promising features have been extensively evaluated in two pivotal trials: EURIDIS (EURopean Trial In Atrial Fibrillation Or Flutter Patients Receiving Dronedarone for the Maintenance of Sinus Rhythm) and ADONIS (American-Australian-African Trial With DronedarONe In Atrial Fibrillation/flutter Patients For The Maintenance of Sinus Rhythm).[16] EURIDIS was performed at 65 centers in 12 European countries and ADONIS at 101 centers in the United States, Canada, Australia, South Africa, and Argentina. Both placebo-controlled, multi-center, multinational, double-blind, parallel-group trials utilized identical protocols to determine the effectiveness of dronedarone in maintaining SR in patients with AF. Patients with at least one documented episode of AF during the previous 3 months and SR for at least 1 hour were randomized to dronedarone 400 mg bid or placebo. Analyses were performed on the intent-to-treat populations (612 and 625 patients in the EURIDIS and ADONIS trials, respectively) to determine the time to AF recurrence over 12 months—the primary study endpoint. When analyzed separately or in combination, dronedarone proved to be superior in maintaining SR with an excellent safety and tolerability profile.[16]

The ANDROMEDA (Antiarrhythmic trial with DROnedarone in Moderate to severe CHF Evaluating morbidity DescreAse) was a placebo-controlled outcome study of dronedarone in patients with a recent episode of decompensated heart failure and a left ventricular ejection fraction (LVEF) < 0.35. A history or the presence of AF was not an inclusion criterion for this study. This trial was stopped by the Data Safety Monitoring Board (DSMB) after recruitment of 627 patients because of excess mortality in the treatment group, compared with the placebo group. Detailed results of this study are yet to be reported and data analysis and interpretation is ongoing at the present time (personal communication: Christian Torp-Petersen).

Design of ATHENA

The ATHENA trial (A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter) is a large outcomes trial to further examine the efficacy and safety of dronedarone in the treatment of AF or atrial flutter (AFL). This study will be of paramount importance for the future of dronedarone. It is a prospective, randomized, placebo-controlled, double-blind, multi-national, multi-center, parallel-group trial evaluating the effects of dronedarone 400mg bid versus placebo (ratio 1:1) over a minimum treatment and follow-up duration of 12 months in patients with paroxysmal or persistent AF/AFL. The trial is registered under ClinicalTrials.gov #NCT 00174785.

The Steering Committee gives advice on the scientific and clinical aspects of the study protocol and related documents and carries the overall responsibility for the execution and scientific reporting of the study. The three amendments to the protocol were based upon recommendations by the Steering Committee and were taken in mutual agreement with the sponsor.

Patient Selection

High-risk patients with a history of paroxysmal or persistent AF/AFL were eligible for participation in ATHENA if they meet the following inclusion criteria: Patients aged 75 years or older were eligible with or without additional risk factors. Alternatively, patients of at least 70 years of age were eligible if one or more of the following risk factors are present: arterial hypertension (ongoing therapy with at least two antihypertensive drugs of different classes); diabetes mellitus; prior stroke or transient ischemic attack or systemic embolism; left atrium diameter greater than or equal to 50 mm by M-mode echocardiography; left ventricular ejection fraction less than 0.40 by 2D-echocardiography. In addition, for each patient one 12-lead ECG within the last 6 months had to be available, showing that the patient had been or was in AF/AFL, and a second 12-lead ECG within the last 6 months, showing that the patient had been or was in SR. Originally, the protocol had allowed patients of younger age with additional risk factors into the study. However, due to the lower than expected mortality figures, the steering committee had recommended to change the inclusion criteria to enrich the risk profile of the overall study population. This protocol amendment was implemented on March 25, 2006.

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Exclusion Criteria

Patients were ineligible for participation in ATHENA if they had one of the following cardiac conditions: Permanent AF, unstable hemodynamic situation (i.e., recently decompensated heart failure); congestive heart failure NYHA class IV; planned major noncardiac or cardiac surgery; acute myocarditis; bradycardia < 50 bpm and/or a PR interval > 0.28 seconds; significant sinus node disease in the past, if not treated with a pacemaker. The following general exclusion criteria were applied: refusal or inability to give informed consent; any noncardiac severe illness limiting life expectancy; pregnancy and breastfeeding; women of childbearing potential without adequate birth control; participation in another clinical trial; patients with a calculated GFR at baseline < 10mL/min using the Cockroft Gault formula; potassium level < 3.5 mmol/L if not corrected. Finally, patients needing concomitant medication which is prohibited within ATHENA (i.e., other antiarrhythmic drugs of Vaughan-Williams class I or III) were excluded.

Study Design

Patients could be included in the study while in SR if conversion has occurred either spontaneously or following electrical or pharmacological cardioversion. Patients also could be included while in AF/AFL, and in this case they could undergo cardioversion after appropriate anticoagulation. Randomization was stratified by center and by the presence or absence of AF/AFL at the time of randomization. After randomization, all patients will be followed until the common study end date; the last patient included in the study will be followed for 1 year. The study will be completed for all patients at this common study end date. Therefore, patients will be followed up for a minimum of 12 months, depending on their time of recruitment into the study. The range of duration of follow-up is anticipated to be 12–30 months.

Study Endpoints

The primary study outcome is the first occurrence of cardiovascular hospitalization or death from any cause during the study period. Any unplanned hospitalization (i.e., admission with an overnight stay in hospital—covering at least 2 consecutive dates) will be categorized depending on the cause and divided into cardiovascular and noncardiovascular. The prespecified main causes for cardiovascular hospitalization are detailed in Table 1.

Deaths will be categorized by a blinded adjudication committee according to a modified Hinkle and Thaler classification[17] into four categories: cardiac death, arrhythmic; cardiac death, nonarrhythmic; vascular death, noncardiac; and noncardiovascular death. This classification scheme has been previously validated in several large trials.[18–20]

Secondary study endpoints are death from any cause; cardiovascular deaths; and hospitalization for cardiovascular reasons.

Sample Size and Statistical Analysis

According to the pooled results of ADONIS and EURIDIS, the 1-year placebo-group cardiovascular hospitalization rate is anticipated to be 20%, a figure that was also observed in the AFFIRM study.[1] Dronedarone reduced the risk of rehospitalization by approximately 20% in the two pivotal efficacy trials. Cardiovascular hospitalization is anticipated to precede the majority of cardiovascular deaths. The remaining deaths, by default deaths not preceded by cardiovascular hospitalization, are unlikely to be influenced by dronedarone. Thus, the overall decrease of risk for the primary endpoint in ATHENA is assumed to be 15% at 1 year. Nine hundred seventy patients reaching the primary endpoint will give 80% power to the trial for testing dronedarone's superiority over placebo at a two-sided 5% alpha-level.

In order to observe about 260 deaths, which will allow to estimate the relative risk of death with a precision of ±0.13, within an inclusion period of 1.5 years, a minimum follow-up of 1 year and a maximum follow-up of 2.5 years (mean follow-up of 1.7 years), enrollment of 2,150 patients per group (4,300 in total) is anticipated to be necessary. All analyses will be done according to the intent-to-treat principle.

Study Progress

Patient enrollment commenced in June 2005. Enrollment of 4,628 patients was completed on December 30, 2006, with planned follow-up expected to end by December 30, 2007. Key baseline demographics of enrolled patients are depicted in Table 2.

Discussion

Antiarrhythmic Drug Therapy in AF

The increasing prevalence of AF due to the aging populations requires development of new effective and safe pharmacological therapies for wide-spread use. At present, amiodarone is the most effective drug for maintaining SR in patients with structural heart disease, but its noncardiac side effects require drug discontinuation in a significant proportion of patients. Dronedarone has similar electrophysiological properties as amiodarone in various experimental settings.[11] In two large pivotal efficacy trials involving 1,237 patients with AF, dronedarone was demonstrated to reduce the risk of recurrent AF by 20–30%.[16] In addition, the drug has marked rate-controlling potency in cases of relapses of AF. Importantly, dronedarone had a very good safety and tolerability profile. Specifically, there was no case of torsade de pointes proarrhythmia reported in the entire clinical development program up to the start of this study. Thus, dronedarone appears to be a promising new antiarrhythmic compound for treatment of AF. Despite the lack of apparent proarrhythmic effects, dronedarone was associated with increased mortality in patients with a recent history of decompensated heart failure (ANDROMEDA). Of note, ANDROMEDA was not an AF study. Although the precise cause for this unexpected observation is at present still unclear, the finding reemphasizes the need for a large dronedarone outcomes study in a typical population of elderly AF patients.

TABLE 1
Main Causes for Cardiovascular Hospitalizations

- Atherosclerosis related (if not otherwise specified)
- Myocardial infarction or unstable angina
- Stable angina pectoris or atypical chest pain
- Syncope
- Transient ischemic attack or stroke (except intracranial hemorrhage)
- Atrial fibrillation and other supraventricular rhythm disorders
- Nonfatal cardiac arrest
- Ventricular arrhythmias
- Cardiovascular surgery except cardiac transplantation
- Cardiac transplantation
- Implantation of a pacemaker, ICD, or any other cardiac device
- Transcutaneous coronary, cerebrovascular, or peripheral procedure
- Blood pressure-related dysfunction, hypertension (except syncope)
- Cardiovascular infection
- Major bleeding (requiring two or more units of blood or any intracranial hemorrhage)
- Pulmonary embolism or deep vein thrombosis
- Worsening congestive heart failure, including pulmonary edema or dyspnea of cardiac origin

TABLE 2
Patient Baseline Data (n = 4,628 Patients)

Baseline Characteristics	Incidence / Mean Value
Patient age	
<65 years	19%
65–74 years	40%
≥75 years	42%
Female gender	47%
Hypertension	86%
Mean systolic blood pressure	134 mmHg
AF at baseline*	25%
History of cardioversion	34%
Structural heart disease**	60%
–History of coronary artery disease	30%
–Ischemic dilated cardiomyopathy	5%
–Nonischemic dilated cardiomyopathy	4%
–Rheumatic valve disease	2%
–Nonrheumatic valve disease	15%
–Hypertrophic cardiomyopathy	2%
–History of congestive heart failure	29%
–LVEF < 0.35	12%
Lone atrial fibrillation***	6%

*AF at baseline according to the stratification factor at randomization.
**Structural heart disease (coronary heart disease and/or ischemic dilated cardiomyopathy and/or nonischemic dilated cardiomyopathy and/or rheumatic valvular heart disease and/or nonrheumatic valvular heart disease and/or hypertrophic cardiomyopathy and/or history of congestive heart failure and/or left ventricular ejection fraction (LVEF) < 45%.
***Lone atrial fibrillation: patients without hypertension and without structural heart disease.

Unique Features of ATHENA

ATHENA is the pivotal outcome study for the development of dronedarone. Several features of this trial deserve further comments. ATHENA is the first large AF trial which does not use any "conventional" endpoint directly related to AF such as prevention of recurrent AF, time to first AF recurrence, AF burden or others.[21] This randomized clinical trial uses for the first time exclusively the combined endpoint of all-cause mortality and rehospitalization for cardiovascular causes. The reason to choose this endpoint is due to the fact that AF represents an increasing socioeconomic burden to Western societies, particularly as a consequence of repeated requirement of arrhythmia-related hospitalizations. Moreover, rehospitalization is one of the major reasons for a significant impairment in quality of life in these patients. Since it was shown that dronedarone is not only capable of maintaining SR in many patients, but also of controlling heart rate in case of AF relapses, it is expected that treatment with this compound will result in a significant reduction in the need of rehospitalizations for cardiovascular reasons.

ATHENA is the largest study ever conducted to evaluate the efficacy and safety of a single antiarrhythmic compound in a typical AF population. More than 4,600 patients have been enrolled in more than 300 investigational sites around the globe. A history of hypertension was the most prevalent underlying cardiovascular disease. 30% of patients had a history of coronary disease, and 29% presented with a previous history of heart failure. The median age of paticits enrolled in the study is 73 years. Therefore, the patients enrolled in ATHENA represent the largest group of individuals seeking medical attention for treatment of AF.

In summary, ATHENA will be the largest antiarrhythmic drug trial conducted in AF. The trial is well powered to establish the efficacy and safety of dronedarone, a new antiarrhythmic compound, for the treatment of AF.

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