

Dronedarone in patients with congestive heart failure: insights from ATHENA

Stefan H. Hohnloser^{1*}, Harry J.G.M. Crijns², Martin van Eickels³,
Christophe Gaudin³, Richard L. Page⁴, Christian Torp-Pedersen⁵,
and Stuart J. Connolly⁶ for the ATHENA Investigators

¹Division of Clinical Electrophysiology, Department of Cardiology, J. W. Goethe University, Theodor-Stern-Kai 7, D 60590 Frankfurt, Germany; ²Department of Cardiology, University Hospital Maastricht, Maastricht, The Netherlands; ³Sanofi Aventis, R&D, Frankfurt, Germany; ⁴University of Washington, Seattle, WA, USA; ⁵Gentofte Hospital, University of Copenhagen, Hellerup, Denmark; and ⁶Population Health Research Institute, McMaster University, Hamilton, Canada

Received 12 November 2009; revised 1 March 2010; accepted 8 March 2010; online publish-ahead-of-print 30 April 2010

Aims

Dronedarone is a new multichannel blocking antiarrhythmic drug for treatment of atrial fibrillation (AF). In patients with recently decompensated congestive heart failure (CHF) and depressed LV function, the drug was associated with excess mortality compared with a placebo group. The present study aimed to analyse in detail the effects of dronedarone on mortality and morbidity in AF patients CHF.

Methods and results

We performed a *post hoc* analysis of ATHENA, a large placebo-controlled outcome trial in 4628 patients with paroxysmal or persistent AF, to evaluate the relationship between clinical outcomes and dronedarone therapy in patients with stable CHF. The primary outcome was time to first cardiovascular (CV) hospitalization or death. There were 209 patients with NYHA class II/III CHF and a left ventricular ejection fraction ≤ 0.40 at baseline (114 placebo, 95 dronedarone patients). A primary outcome event occurred in 59/114 placebo patients compared with 42/95 dronedarone patients [hazard ratio (HR) 0.78, 95% CI = 0.52–1.16]. Twenty of 114 placebo patients and 12/95 dronedarone patients died during the study (HR 0.71, 95% CI = 0.34–1.44). Fifty-four placebo and 42 dronedarone patients were hospitalized for an intermittent episode of NYHA class IV CHF (HR = 0.78, 95% CI = 0.52–1.17).

Conclusion

In this post-hoc analysis of ATHENA patients with AF and stable CHF, dronedarone did not increase mortality and showed a reduction of CV hospitalization or death similar to the overall population. However, in the light of the ANtiarrhythmic trial with DRonedarone in Moderate to severe CHF Evaluating morbidity DecreAse study, dronedarone should be contraindicated in patients with NYHA class IV or unstable NYHA classes II and III CHF.

Keywords

Atrial fibrillation • Congestive heart failure • Dronedarone

Introduction

Dronedarone is a new multichannel blocking antiarrhythmic drug for the treatment of patients with atrial fibrillation (AF). Two large randomized placebo-controlled trials have demonstrated the rhythm-controlling efficacy of the compound.¹ In addition, dronedarone has been shown to have rate-controlling properties in patients with permanent AF.² In ATHENA [A placebo-controlled, double-blind, parallel arm trial to assess the efficacy of

dronedarone 400 mg bid for the prevention of cardiovascular (CV) hospitalization or death from any cause in patients with AF/atrial flutter (AFL)], a large outcome trial in 4628 patients, dronedarone reduced major clinical outcomes in patients with AF including CV hospitalizations, CV mortality, and stroke.³ However, the ANDROMEDA [ANtiarrhythmic trial with DRonedarone in Moderate to severe congestive heart failure (CHF) Evaluating morbidity DecreAse] study in patients with recently decompensated heart failure and depressed left ventricular

* Corresponding author. Tel: +49 69 6301 7404, Fax: +49 69 6301 7017, Email: Hohnloser@em.uni-frankfurt.de

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2010. For permissions please email: journals.permissions@oxfordjournals.org. The online version of this article has been published under an open access model. Users are entitled to use, reproduce, disseminate, or display the open access version of this article for non-commercial purposes provided that the original authorship is properly and fully attributed; the Journal, Learned Society and Oxford University Press are attributed as the original place of publication with correct citation details given; if an article is subsequently reproduced or disseminated not in its entirety but only in part or as a derivative work this must be clearly indicated. For commercial re-use, please contact journals.permissions@oxfordjournals.org

Table 1 Hazard ratios for the primary study endpoint for patients treated with dronedarone in relation to the presence or absence of congestive heart failure and of impaired left ventricular ejection fraction

Patient group	P (n)	D (n)	Hazard ratio	95% confidence interval	P-value for interaction
Patients without CHF	1634	1629	0.76	0.68–0.86	0.22
Patients with CHF NYHA I/II	584	581	0.80	0.67–0.96	
Patients with CHF NYHA III	109	91	0.56	0.38–0.82	
Patients with LVEF ≤ 0.40	184	154	0.72	0.51–1.00	0.67
Patients with LVEF > 0.40	2097	2109	0.77	0.69–0.85	

P, placebo; D, dronedarone.

function was stopped prematurely due to excess mortality in the dronedarone arm relative to the placebo group.⁴ The reasons for the observed excess mortality have not been fully elucidated.

In order to investigate in more detail the effects of dronedarone in AF patients with stable CHF, we performed an exploratory analysis of ATHENA to evaluate the relationship between clinical outcomes and dronedarone therapy in this important subpopulation of patients.

Methods

The design and the primary results of the ATHENA trial have been previously published.^{3,5} In short, patients with paroxysmal or persistent AF and at least one additional risk factor for CV events including age ≥ 75 years or < 75 years with one or more of the following risk factors: hypertension, diabetes mellitus, prior stroke or TIA, left atrial enlargement (≥ 50 mmHg), or depressed left ventricular ejection fraction (LVEF) (≤ 0.40) were eligible. They were randomized to receive dronedarone 400 mg bid or matching placebo. Main exclusion criteria were unstable haemodynamic condition, such as CHF of NYHA functional class IV within 4 weeks, and presence of permanent AF. The follow-up visit schedule included clinical evaluations at days 7 and 14 and at months 1, 3, 6, 9, 12 and every 3 months thereafter. In the case of clinical deterioration, patients were seen as indicated clinically. At each visit, a physical examination was performed and a 12-lead electrocardiogram (ECG) was recorded at each visit up to 6 months and every 6 months thereafter.

The primary outcome measure was time to first CV hospitalization or death [hazard ratio (HR) = 0.76, 95% CI = 0.69–0.84, $P < 0.001$].³ Pre-specified secondary outcome measures were total mortality (HR = 0.84, 95% CI = 0.66–1.08, $P = 0.18$), CV mortality (HR = 0.71, 95% CI = 0.51–0.98, $P = 0.03$), and CV hospitalization (HR = 0.74, 95% CI = 0.67–0.82, $P < 0.001$).³ Deaths were categorized by a blinded Adjudication Committee into four categories: cardiac arrhythmic; cardiac non-arrhythmic; vascular non-cardiac; and non-vascular. Information on the occurrence of new or worsened CHF was gathered from hospitalization and death reports which included specific information on the occurrence of CHF.

Analyses were performed on the intention-to-treat population. The time to event was estimated according to the non-parametric Kaplan–Meier method and compared by a two-sided log-rank's asymptotic test. Hazard ratio was calculated using Cox's proportional hazard model with treatment group as covariate. Interactions between several subgroups were tested using a likelihood ratio test. All P -values were two-tailed and threshold used for significance was

0.05. Statistical analyses were done using SAS version 8.2 on UNIX environment.

Results

A total of 4628 patients were enrolled in ATHENA with 2301 assigned to dronedarone and 2327 to placebo. Overall, there was no significant interaction between the treatment effects of dronedarone and the presence or absence of a history of CHF or impaired left ventricular function (Table 1).

Patients with NYHA class II/III and left ventricular ejection fraction ≤ 0.40

A total of 209 patients with stable CHF NYHA functional class II or III in the setting of a documented LVEF ≤ 0.40 were enrolled in ATHENA. Of these, 114 were assigned to receive placebo and 95 to receive dronedarone. Compared with the overall patient population, these patients had more often coronary artery disease, ischaemic or non-ischaemic cardiomyopathy, and were more often having a permanent pacemaker or an implanted defibrillator (Table 2). As summarized in Figures 1 and 2 and Table 3, the results for all outcome measures in this patient population were consistent with those observed in the overall population, with fewer events in the dronedarone compared with the placebo group. Furthermore, in this subgroup, outcomes were not related to impairment in renal function. The HR for dronedarone in terms of all-cause mortality was 0.71 (95% CI = 0.33–1.55) for patients with a creatinine clearance (determined by the Cockcroft Gault formula) of < 65 mL/min and 0.75 (95% CI = 0.13–4.51) for those with a clearance of ≥ 65 mL/min (P -value for interaction 0.98).

Treatment-emergent adverse events (adverse events occurring between first study drug intake and last study drug intake +10 days) occurred in 90 of 114 placebo patients (78.9.2%) and in 65 of 95 dronedarone patients (58.4%). Serious treatment-emergent adverse events occurred in 28.1% of placebo patients and in 16.8% of dronedarone patients. The most frequent adverse events were infections and gastrointestinal disorders that occurred at similar rates in the dronedarone group. The overall adverse event profile was similar to the overall patient population with bradycardia (placebo 0.9% and dronedarone 3.2%), QT-interval prolongation (placebo 2.6% and dronedarone 4.2%), creatinine increase (placebo 2.6% and dronedarone 10.5%), nausea

Table 2 Selected demographics for patients in NYHA functional class II or III and with left ventricular ejection fraction ≤ 0.40 at baseline

	NYHA II/III patients with LVEF ≤ 0.40 at baseline		Remaining patients	
	Placebo (n = 114)	Dronedarone (n = 95)	Placebo (n = 2167)	Dronedarone (n = 2168)
Age (years; SD)	72.0 (8.5)	71.3 (9.5)	71.7 (9.0)	71.6 (8.9)
Male gender (%)	81 (71.1%)	71 (74.7%)	1186 (54.7%)	1075 (49.6%)
Hypertension	86 (75.4%)	75 (78.9%)	1876 (86.6%)	1892 (87.3%)
Coronary heart disease	67 (58.8%)	51 (53.7%)	647 (29.9%)	600 (27.7%)
Ischaemic dilated cardiomyopathy	36 (31.6%)	35 (36.8%)	80 (3.7%)	57 (2.6%)
Non-rheumatic valvular heart disease	27 (23.7%)	28 (29.5%)	321 (14.8%)	300 (13.8%)
Non-ischaemic dilated cardiomyopathy	25 (21.9%)	18 (18.9%)	58 (2.7%)	62 (2.9%)
Pacemaker	23 (20.2%)	23 (24.2%)	215 (9.9%)	188 (8.7%)
Implanted cardioverter defibrillator	22 (19.3%)	19 (20.0%)	20 (0.9%)	23 (1.1%)

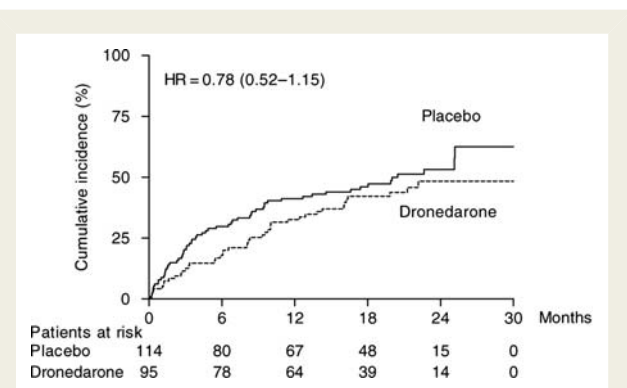


Figure 1 Kaplan–Meier cumulative incidence curves of time to first cardiovascular hospitalization or death in patients with NYHA II/III congestive heart failure and left ventricular ejection fraction ≤ 0.40 at baseline assigned to dronedarone or placebo.

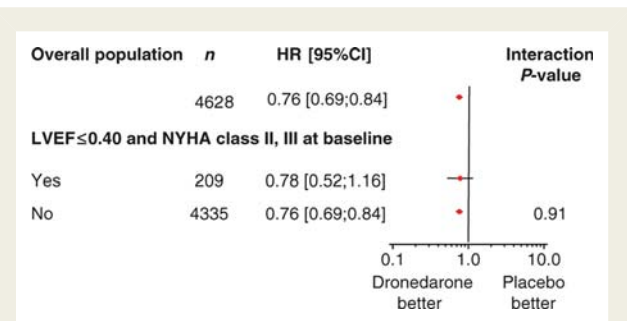


Figure 2 Forrest plot for first cardiovascular hospitalization or death in the overall ATHENA population and patients with or without NYHA II/III congestive heart failure and left ventricular ejection fraction ≤ 0.40 at baseline.

(placebo 4.4% and dronedarone 8.4%), diarrhea (placebo 9.6% and dronedarone 14.7%), and rash (placebo 0% and dronedarone 3.2%). Fourteen patients in the placebo group (12.3%) and 18 dronedarone patients (18.9%) permanently discontinued study drug

due to adverse events. The dronedarone-mediated increase in serum creatinine was similar to the overall ATHENA population (Figure 3).

Patients developing clinical instability during follow-up

In ATHENA, an analysis of time to first hospitalization for heart failure included 132 events in the placebo group vs. 112 events in the dronedarone group (HR = 0.85, 95% CI = 0.66–1.10).³ When patients were further followed after this hospitalization, 12 patients died in the dronedarone group compared with 26 in the placebo group.

A further analysis concerned those patients who developed an episode of NYHA functional class IV CHF during the course of the study. Fifty-four placebo and 42 dronedarone patients were hospitalized while in CHF class IV (HR = 0.78, 95% CI = 0.52–1.17). The median time from randomization to hospitalization with NYHA class IV CHF was 227 days in the placebo arm and 228 days in the dronedarone arm, respectively. Patients with NYHA class IV CHF episodes were older, had more structural heart disease (notably coronary disease and ischaemic cardiomyopathy), and less lone AF compared with patients without such episodes. When patients were further followed after in-hospital resolution of CHF, 15 placebo patients and 10 dronedarone patients died.

Discussion

The present exploratory analysis of ATHENA demonstrates a lack of excess mortality or morbidity in AF patients with stable CHF treated with dronedarone. In fact, consistent with the results of the main trial,³ therapy with dronedarone was associated with a decrease in the primary study outcome in patients with NYHA functional class III CHF at baseline. Similarly, in patients with NYHA class II/III CHF and a LVEF ≤ 0.40 , representing the sub-population with systolic heart failure, event rates were not different in the dronedarone and the placebo groups.

Table 3 Outcome measures in patients in NYHA functional class II or III and with left ventricular ejection fraction ≤ 0.40 at baseline

Outcome measure	Placebo (n = 114)	Dronedaron (n = 95)	Hazard ratio (95% CI)
Time to first CV hospitalization or death from any cause	59	42	0.778 (0.523, 1.156)
First CV hospitalization	48	35	0.793 (0.523, 1.156)
Death from any cause	20	12	0.705 (0.344, 1.442)
First hospitalization for CHF or CV death	27	21	0.898 (0.507, 1.589)

CV, cardiovascular; CHF, congestive heart failure; CI, confidence interval.

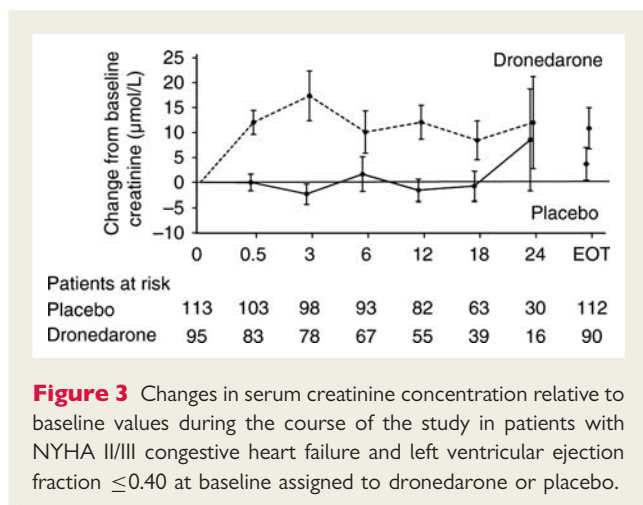


Figure 3 Changes in serum creatinine concentration relative to baseline values during the course of the study in patients with NYHA II/III congestive heart failure and left ventricular ejection fraction ≤ 0.40 at baseline assigned to dronedaron or placebo.

Antiarrhythmic drug therapy in atrial fibrillation patients with congestive heart failure

Most antiarrhythmic drugs are not recommended for the treatment of AF in the setting of CHF and/or depressed LV function because these patients are particularly prone to ventricular proarrhythmic effects and to negative inotropic action of antiarrhythmic drugs. Current guidelines for the treatment of AF recommend only the use of amiodaron or dofetilide in heart failure patients with AF.⁶ Whereas amiodaron is well tolerated in patients with impaired LV function⁷ and has very little proarrhythmic side effects,⁸ its use is hampered by the extracardiac side effects that can be serious and necessitate discontinuation in a significant proportion of patients. Dofetilide, on the other hand, carries a significant proarrhythmic potential⁹ which is why the drug has to be initiated in-hospital with ECG monitoring for at least a few days. For this reason dofetilide is not marketed in all countries. The lack of safe and efficacious pharmacological treatment options for AF in the setting of CHF warrants careful evaluation of new antiarrhythmic compounds.

Dronedaron for therapy of atrial fibrillation in congestive heart failure

A previous study in CHF patients using dronedaron, ANDROMEDA, was terminated prematurely due to the observation of increased mortality with dronedaron.⁴ ANDROMEDA enrolled

patients with advanced CHF characterized by LVEF ≤ 0.35 and, importantly, a recent hospitalization with new or worsening heart failure. There were 627 patients enrolled and followed for a median of 2 months. Thirteen excess deaths occurred on dronedaron (HR = 2.13, 95% CI = 1.07–2.45, $P = 0.03$). The excess mortality was predominantly related to CHF (10 deaths vs. 2). This finding contrasts the results of ATHENA where dronedaron reduced CV mortality.³ Specifically, ATHENA demonstrated in 4628 patients with AF at moderate to high risk for CV events that dronedaron therapy was not associated with increased mortality due to pump failure (HR = 0.95, 95% CI = 0.41–1.85, $P = 0.89$) or with an increase in hospitalizations for CHF (HR = 0.86, 95% CI = 0.67–1.10, $P = 0.22$).³ The present analysis extends these observations and yields results for the population with stable class II/III CHF in the setting of reduced LVEF. All findings are consistent with the overall observations made in ATHENA. Even in these high-risk subsets, there was no sign of harm associated with dronedaron therapy.

How can we understand the difference between ATHENA and ANDROMEDA? There were 356 NYHA class III patients in ANDROMEDA⁴ compared with 200 such patients in ATHENA. On the other hand, ATHENA included 80 times more patient years of exposure to dronedaron than ANDROMEDA. The presence or absence of clinical stability was the primary feature that distinguished patients enrolled in the ANDROMEDA and ATHENA trials. Specifically, the ANDROMEDA trial was conceptualized primarily as a study that sought to enrol clinically unstable patients with advanced heart disease; as such, this trial enrolled patients who might be most likely to demonstrate a proarrhythmic effect of dronedaron (if one existed). In contrast, the ATHENA trial was conceptualized primarily as an efficacy study and sought to enrol patients likely to receive the drug in clinical practice, i.e. those with recent or current AF/AFL. Although most of the patients in the ATHENA trial had structural heart disease, they were clinically stable. Both trials enrolled patients with low ejection fractions or with NYHA class II or III heart failure; however, these patients had been hospitalized for worsening heart failure in the ANDROMEDA trial but were stable outpatients in the ATHENA trial. The observation of a higher mortality rate in ANDROMEDA is in line with a recent analysis of a large heart failure trial.¹⁰ Solomon et al. elucidated the subsequent risk of death associated with a heart failure admission (which all patients enrolled in ANDROMEDA were required to have). They found that the mortality rate was highest early after a heart failure hospitalization and

declined thereafter but never reached the relative risk obtained in patients without a heart failure hospitalization.¹⁰ These data suggest that patients with CHF are most vulnerable in the immediate aftermath of a hospital admission and should therefore not receive dronedarone during this period.

Both ANDROMEDA and ATHENA observed an increase in serum creatinine in patients receiving dronedarone. It is possible that investigators observing a creatinine increase in ANDROMEDA due to dronedarone inappropriately discontinued angiotensin-converting enzyme inhibitor therapy which might have resulted in worsening of CHF. Therefore, ATHENA investigators were informed that a small rise in creatinine due to a specific partial inhibition of tubular organic cation transporters¹¹ was expected with dronedarone not indicating a decline in renal function.

Limitations of the study

Exploratory efficacy analyses comprising relatively small subgroups have inherent limitations that result from the loss of a randomization effect. We also acknowledge the fact that the interaction analyses may be underpowered given the small patient numbers in some of the subgroups. However, the consistency of our analyses suggests that our findings are robust.

Clinical implications

While patients with unstable haemodynamic conditions were excluded from ATHENA, patients with stable CHF at baseline showed results that were consistent with those observed in the overall ATHENA population. In patients with AF and stable CHF, dronedarone did not increase mortality and showed a trend towards the reduction of CV hospitalization or death. There was no increase in CHF hospitalizations in the dronedarone arm. According to the ANDROMEDA study, however, dronedarone is contraindicated in patients with NYHA class IV heart failure or unstable NYHA classes II and III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic.

Acknowledgement

The trial is registered under ClinicalTrials.gov #NCT 00174785. The trial was sponsored by Sanofi Aventis, Paris, France.

Funding

Funding to pay the Open Access publication charges for this article was provided by sanofi-aventis.

Conflicts of interest: S.H.H reports receiving consulting fees from Sanofi Aventis, Cardiome, ARYx, BMS, research grants from Sanofi

Aventis and St. Jude Medical, and lecture fees from Sanofi Aventis, St. Jude Medical, and BMS; H.J.G.M.C., consulting fees from Medacorp, Astra Zeneca, Sanofi Aventis, Cardiome, research grants from Astra Zeneca and St. Jude Medical, and lecture fees from Astra Zeneca, Sanofi Aventis, and Chugai Pharmaceuticals; R.L.P., consulting fees from Sanofi Aventis, Astellas, and Pfizer; C.T.-P., consulting fees from Sanofi Aventis and Cardiome, research grants from Sanofi Aventis, lecture fees from Sanofi Aventis and Cardiome; S.J.C., consulting fees and research grants from Sanofi Aventis. M.E. and C.G. are employees of Sanofi Aventis and own Sanofi Aventis shares.

References

1. Singh BN, Connolly SJ, Crijns HJ, Roy D, Kowey P, Capucci A, Radzik D, Aliot E, Hohnloser SH. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. *N Engl J Med* 2007;**357**:987–999.
2. Davy JM, Herold M, Hognlund C, Timmermans A, Alings A, Radzik D, Van Kempen L, ERATO Study Investigators. Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the Efficacy and safety of dRonedArone for the cOntrol of ventricular rate during atrial fibrillation (ERATO) study. *Am Heart J* 2008;**156**:527. e1-9.
3. Hohnloser SH, Crijns HJGM, van Eickels M, Gaudin C, Page R, Torp-Pedersen C, Connolly S. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med* 2009;**360**:668–678.
4. Kober L, Torp-Pedersen C, McMurray JJV, Gotzsche O, Levy S, Crijns H, Amle J, Carlsen J, for the dronedarone study group. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008;**358**:2678–2687.
5. Hohnloser SH, Connolly SJ, Crijns HJ, Page RL, Seiz W, Torp-Petersen C. 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. *J Cardiovasc Electrophysiol* 2008;**19**:69–73.
6. Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA. ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006;**114**:e257–e354.
7. Singh SN, Fletcher RD, Fisher SG, Singh BN, Lewis HD, Deedwania PC, Massie BM, Colling C, Lazzeri D, for the Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure. Amiodarone in patients with congestive heart failure and asymptomatic ventricular arrhythmias. *N Engl J Med* 1995;**333**:77–82.
8. Hohnloser SH, Klingenhoben T, Singh BN. Amiodarone-associated proarrhythmic effects: a review with special reference to torsades de pointes tachycardia. *Ann Int Med* 1994;**121**:529–538.
9. Pedersen OD, Bagger H, Keller N, Marchant B, Kober L, Torp-Pedersen C, for the Danish Investigations of Arrhythmia, Mortality on Dofetilide Study Group. Efficacy of dofetilide in the treatment of atrial fibrillation-flutter in patients with reduced left ventricular function. *Circulation* 2001;**104**:292–296.
10. Solomon SC, Dobson J, Pocock S, Skali H, McMurray JJV, Michelson EL, Pfeffer MA, for the CHARM Investigators. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation* 2007;**116**:1482–1487.
11. Tschuppert Y, Buclin T, Rothuizen LE, Decosterd LA, Galleyrand J, Gaud C, Biollaz J. Effect of dronedarone on renal function in healthy subjects. *Br J Clin Pharmacol* 2007;**64**:785–791.