Atrial fibrillation

An individual patient-based meta-analysis of the effects of dronedarone in patients with atrial fibrillation

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Aims

Dronedarone is a non-iodinated benzofuran derivative with antiarrhythmic properties. In placebo-controlled atrial fibrillation (AF) trials, the drug was found to have divergent effects on endpoints such as cardiovascular death or hospitalization. The objective of this meta-analysis of all placebo-controlled studies was to provide insights on possible reasons for these divergent effects.

Methods and results

Individual data on 9664 patients were used from all AF placebo-controlled studies. The primary outcome measure was cardiovascular death. Cardiovascular hospitalization and hospitalization for heart failure were secondary endpoints. Pre-defined procedures were used to reduce inter-study heterogeneity adjusting for important baseline variables using a Cox model. Despite adjustments, a significant inter-trial heterogeneity of the outcome of cardiovascular mortality persisted (P-value of 0.005 for the treatment effect × study interaction). Further analyses were conducted in subgroups based on baseline clinical criteria: digoxin co-prescription, advanced heart failure, coronary artery disease, or the presence of permanent AF. These analyses allowed the calculation of a global treatment effect in two important patient subgroups, those with permanent AF in whom there was harm with respect to cardiovascular mortality [hazard ratio (HR) = 2.32; 95% confidence interval (CI) 1.13–4.75] and hospitalization for heart failure (HR = 1.674; 95% CI 1.05–2.67); and those with non-permanent AF in whom there was benefit in terms of cardiovascular hospitalization [HR = 0.751 95% CI (0.68–0.83)].

Conclusion

This meta-analysis demonstrates significant heterogeneity of dronedarone treatment effects across the placebo-controlled randomized trials. The most important predictor of a harmful effect of dronedarone on cardiovascular death and heart failure hospitalization was the presence of permanent AF.

Keywords

Atrial fibrillation ● Dronedarone ● Randomized clinical trials

Introduction

Dronedarone is a benzofuran derivative with antiarrhythmic properties. Like amiodarone, dronedarone possesses Class I–IV antiarrhythmic activity on the Vaughan–Williams classification scheme, antiadrenergic effects and antifibrillatory effects on the atrial and ventricular myocardium but no iodine-related organ toxicity, a decreased lipophilicity and a shortened half-life.

The ATHENA trial, conducted in patients with paroxysmal or persistent atrial fibrillation (AF), demonstrated important beneficial effects of dronedarone. The primary endpoint—composite of all-cause mortality or first unscheduled cardiovascular hospitalization—was significantly reduced in patients on dronedarone compared with placebo. Other types of outcomes including arrhythmic death, stroke, or acute coronary syndromes were also significantly reduced. The reduction in the primary outcome was consistent in all patient subgroups examined. In contrast, the PALLAS trial was conducted in patients with permanent AF with a high burden of concomitant cardiovascular morbidity. This trial was stopped prematurely after inclusion of 3236 patients due to a highly significant

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What’s new?

- This is a meta-analysis of all placebo-controlled atrial fibrillation trials of dronedarone based on individual data from 9664 patients.
- Despite careful adjustments for potential confounders, a significant inter-trial heterogeneity of the outcome of cardiovascular mortality persisted.
- Our analyses allowed the calculation of a global treatment effect in 2 important patient subgroups, those with permanent AF in whom there was harm with respect to cardiovascular mortality and hospitalization for heart failure; and those with non-permanent AF in whom there was benefit in terms of cardiovascular hospitalization.

Excess of stroke, cardiovascular death, cardiovascular hospitalization, and heart failure events.

The reasons for this apparent discrepancy of the results of these two dronedarone trials are unclear. Accordingly, the present meta-analysis of all randomized controlled AF trials of dronedarone was conducted for three purposes: (i) to summarize the totality of data on the efficacy and safety of dronedarone in patients with AF; (ii) to test the various trials for heterogeneity in important outcome events; and (iii) to discern reasons for the unexpected findings of the PALLAS trial.

Methods

This meta-analysis complies with the guidelines provided by the Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 (http://www.cochrane-handbook.org/) and the QUORUM guidelines for the conduct of meta-analyses reporting results from randomized clinical trials.

Data sources and selection of studies

A comprehensive literature search was conducted to identify all randomized placebo-controlled Phase II and III studies of the efficacy and safety of dronedarone in patients with AF or flutter. The following criteria were used for inclusion of trials: (i) prospective, randomized, placebo-controlled study design; (ii) population with AF or flutter; (iii) individual patient-based data on all-cause- and cardiovascular mortality available for the study. The literature search identified 89 dronedarone publications. Of these, 82 trials had to be excluded because they did not meet the pre-specified inclusion criteria.

Seven dronedarone placebo-controlled studies were finally selected for this meta-analysis: DAFNE—The Dronedarone Atrial Fibrillation study after Electrical Cardioversion, EURIDIS—The EURopean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm, NCT00259428, ADONIS—The American–African trial with Dronedarone in Moderate-to-severe CHF Evaluating morbidity Decrease, NCT00543699. In this study, AF was not a mandatory inclusion criterion but 157 of 627 enrolled patients (25%) had AF at baseline. Only the subgroup of patients with AF at inclusion was included in this meta-analysis.

Outcome measures

The main clinical endpoint of the present analysis, cardiovascular mortality, was centrally adjudicated using a procedure specific to each study but which in general included deaths associated with arrhythmia occurring unexpectedly in a previously stable patient, deaths from heart failure, deaths from cerebrovascular accidents, and deaths from other cardiac causes such as pulmonary embolism, dissection or rupture of aortic or arterial aneurysm, myocardial rupture, pericardial tamponade, valve thrombosis, or as a direct consequence (e.g. bleeding) of a cardiac invasive intervention or surgery. Other endpoints of interest were cardiovascular hospitalization and hospitalization for heart failure. In the ATHENA, PALLAS, and ANDROMEDA trials, fatal events were centrally adjudicated into cardiovascular and non-cardiovascular causes by adjudication committees which were blinded as to the assignment of patients to active therapy with dronedarone or placebo. In DAFNE, EURIDIS/ADONIS, ERATO fatal events were classified post hoc by a subgroup of the authors of this manuscript.

Statistical methods

For all trials, individual patient data were entered in a central database which was kept by the sponsor of the studies (Sanofi-Aventis). Accordingly, all analyses were conducted using individual patient data from each study. This sometimes required going back to the original case record forms to extract relevant information. All analyses are based on the intention-to-treat principle. Studies with no endpoint event in one group were excluded from the analyses of this endpoint to avoid estimation issues. Patients with missing values for one of the covariates were excluded from the analysis.

For each endpoint, a stepwise selection of the important covariates—forward selection plus backward elimination—was applied to reduce the inter-study heterogeneity by adjusting for important patient characteristics. For this purpose, a Cox model was used including only patient characteristics as covariates (gender, LVEF, NYHA class, history of diabetes, hypertension, stroke/TIA, or coronary artery disease (CAD), resting heart rate, treatment with diuretics, anticoagulants, and creatinine clearance). The model criterion for entry was a P-value of < 0.25, and for elimination a P-value of > 0.10. Then the selected model was run adding the treatment variable to estimate treatment effect in each study adjusted on patient characteristics from the Cox model. A general fixed-effect parametric approach was used and the interaction between treatment and studies was tested. When no interaction was detected, a global treatment effect was estimated. A P-value of 0.10 was conservatively defined to have a good power of detection of a significant treatment effect x studies interaction, as per the Cochrane guidelines (http://www.cochrane-handbook.org/).

When significant inter-study heterogeneity was identified, potential sources of heterogeneity were examined by performing subgroup analysis using variables predefined by the authors of this manuscript. These were considered to be a likely source of heterogeneity because of their recognized prognostic importance. The following subgroups were explored depending on patient characteristics assessed at baseline, before study drug initiation:
Results

Study characteristics

Of the seven trials selected, three comprised patients with paroxysmal or persistent AF in whom dronedarone was tested for maintenance of sinus rhythm (DAFNE, EURIDIS, ADONIS). A small study (ERATO) enrolled patients with permanent AF in whom dronedarone was used for rate control. Two large outcome trials, one in patients with paroxysmal/persistent AF (ATHENA) and one in patients with permanent AF (PALLAS), evaluated the effects of the compound on cardiovascular endpoints including mortality. Finally, one trial (ANDROMEDA) enrolled patients with recently decompensated heart failure and evaluated dronedarone with respect to all cause mortality. There were more comorbidities in patients enrolled in the ANDROMEDA and in the PALLAS trial when compared with the other studies. Details of patients’ demographics and baseline medications from these seven trials are given in Table 1.

ANDROMEDA and PALLAS comprised the highest proportion of patients with more advanced classes of CHF: all patients in ANDROMEDA had CHF NYHA ≥ II per inclusion criterion, while the proportion of patients with CHF NYHA ≥ I was 54% in PALLAS, 28% in ERATO, 21% in ATHENA, and <13% in the remaining studies.

ANDROMEDA and PALLAS also comprised the highest proportion of patients with severe left ventricular dysfunction. All patients in ANDROMEDA had an LVEF ≤ 35% as part of the inclusion criteria, while the proportion of patients with LVEF ≤ 40% was 22.8% in PALLAS, 11.6% in ERATO, 9.3% in ATHENA, and ≤8% in the remaining studies.

There were also differences in concomitant medications at baseline. Consistent with a higher proportion of patients with more advanced CHF and severe left ventricular dysfunction, more patients were treated with angiotensin I-converting enzyme (ACE)-inhibitors/angiotensin II receptor blockers (ARBs) and diuretics in ANDROMEDA and PALLAS compared with the other studies. Digitalis glycosides were most frequently prescribed in ANDROMEDA and in the two permanent AF studies, ERATO and PALLAS.

For each study, the observation period lasted from randomization to a cut-off date which depended on the study duration: 6 months in DAFNE and ERATO, 12 months in EURIDIS and ADONIS, last patient last visit in ATHENA (median = 21.7 months), and randomization to premature study drug discontinuation in ANDROMEDA (median = 7.6 months) and PALLAS (median = 3.9 months). The median study duration varied between 31 and 651 days (Table 1).

Cardiovascular mortality

The selected studies comprised 218 cardiovascular deaths yielding an incidence rate of 2.27 events per 100 patient-years in the placebo group and 2.13 per 100 patient-years in the dronedarone group (Table 2). Hazard ratios and confidence intervals (95% CIs) varied widely between trials indicating benefit of dronedarone [0.584 (0.19–1.84) in ADONIS and 0.785 (0.57–1.09) in ATHENA] or evidence of harm [2.186 (1.03–4.64) in PALLAS and 4.802 (1.35–17.06) in ANDROMEDA]. The ATHENA trial contributed the highest number of fatal events, representing ~70% of all cardiovascular deaths.

Although cardiovascular mortality was the primary endpoint of this study, we looked at all-cause death as well: In the overall patient population, the majority of deaths were of cardiovascular origin, 66 and 65% in the placebo and the dronedarone group, respectively. The incidence of all-cause mortality was 3.43 and 3.29 per 100 patient-years in subjects randomized to placebo and dronedarone, respectively.

Despite adjustment for important baseline characteristics such as gender, LVEF, NYHA class, history of diabetes, hypertension, stroke/TIA, or CAD, resting heart rate, treatment with diuretics, anticoagulants, and creatinine clearance, a significant inter-trial heterogeneity of the outcome of cardiovascular mortality was present as expressed by a significant P-value of 0.005 for the treatment effect × study interaction. Heterogeneity was confirmed by the Galbraith analysis (see Supplementary material online, Figure S1), showing that ANDROMEDA and PALLAS trial results for this endpoint fell outside the upper 95% confidence limit of the homogeneity area, while ADONIS and ATHENA trial results were within this area. Given the observed significant inter-study heterogeneity in outcomes, an overall treatment effect of dronedarone could not be calculated.

In an attempt to further elucidate potential sources of heterogeneity, analyses of four key subgroups (patients with/without permanent AF, patients with/without CAD, patients with/without CHF, patients with/without concomitant digoxin therapy) were performed. The heterogeneity among studies was still present in most of the subgroups as documented by an interaction treatment × study P-value of <0.05. When such an interaction existed an overall treatment effect hazard ratio (HR) is difficult to interpret, because of the differences between studies and the 95% CI of the HR calculated using the random-effect approach rather than the point estimate should be taken into consideration (Table 3).

The overall treatment effect HR was calculated and is presented in Table 3 in those subgroups where no interaction × study was observed. Based on these results, the strongest predictor of a harmful effect of dronedarone on cardiovascular death was the presence of permanent AF since only in this group there was a significant treatment effect as indicated by a 95% CI excluding 1 (HR 2.32, 95% CI 1.13–4.75).

The analysis according to digoxin use showed a trend to increased risk of cardiovascular death on dronedarone (HR 2.16, 95%CI 0.71–6.54) compared with the patient not on digoxin in whom there was
no evidence for increased risk of cardiovascular death (HR 0.76, 95% CI 0.55–1.04).

**Cardiovascular hospitalization**

All seven studies were entered into the model for this endpoint. A total of 1966 patients had at least one cardiovascular hospitalization yielding an incidence of 26.93 events per 100 patient-years in the placebo group and 21.74 per 100 patient-years in the dronedarone group (Table 2).

The inter-trial heterogeneity was confirmed by a treatment effect × study interaction P-value of <0.001. This heterogeneity was corroborated by the Galbraith analysis: PALLAS fell outside the 95% CI of the homogeneity area while the other six studies were within this range.

In five of the studies, the point estimate of the HR was in favour of dronedarone for this endpoint in comparison to placebo with a HR (95% CI) ranging from 0.352 (0.07–1.75), NS in ERATO to 0.750 (0.57–0.98), NS in ATHENA. In two studies, the HR point estimate indicated harm of dronedarone relative to placebo with a HR (95% CI) of 1.388 (0.78–2.47), NS in ANDROMEDA and 1.932 (1.41–2.65), P < 0.001 in PALLAS.

To further explore the significant inter-trial heterogeneity for this endpoint, the same approach used for cardiovascular mortality was used separating patients into four key subgroups (patients with/without permanent AF, patients with/without CAD, patients with/without CHF, patients with/without concomitant digoxin therapy). A significant treatment × study interaction P-value persisted in all subgroups with the exception of patients with digoxin at baseline.
and those with non-permanent AF (Table 4). An overall HR for treatment effect could therefore be estimated in these two subgroups: while in the subgroup of patients with digoxin at baseline the HR (95% CI) showed no significant treatment effect 0.844 (0.68–1.05), as indicated by the 95% CI including 1, a statistically significant effect in favour of dronedarone was, on the other hand, observed in the subgroup of patients with non-permanent AF [HR = 0.751 (0.68–0.83)], indicating that dronedarone prevents CV hospitalization in this subgroup of patients consistently across the different trials.

**Hospitalization for heart failure**

There were a total of 377 patients with at least one hospitalization for heart failure in the selected studies yielding an incidence of 3.89 events per 100 patient-years in the placebo group and 3.91 per 100 patient-years in the dronedarone group (Table 2).

Five studies could be entered into the model: DAFNE, ADONIS, ANDROMEDA, ATHENA, and PALLAS (see Supplementary material online, Table S5).

There was a modest heterogeneity among studies on this endpoint despite the adjustment on patient characteristics (P = 0.081). Heterogeneity was confirmed by the Galbraith analysis where PALLAS fell outside the 95% CI of the homogeneity area, while the other four studies were within this range. Because of this heterogeneity, a global treatment effect could not be estimated but the effect in each study was analysed. In one of the studies, PALLAS, the HR (95% CI) for this endpoint indicated harm in patients treated with dronedarone in comparison with placebo: 1.918 (1.15–3.19), while in the other studies the increase in heart failure hospitalization did not reach statistical significance. ATHENA was the only study where the HR (95% CI), 0.875 (0.68–1.13), favoured dronedarone in comparison with placebo although this decrease in hospitalizations for heart failure did not reach statistical significance.

To further explore the reasons for the difference between studies, the same approach used for cardiovascular mortality and CV hospitalization was used, separating patients into four key subgroups. After this separation within each subgroup, no significant heterogeneity was observed (interaction treatment × study P > 0.10), therefore a global HR could be estimated using the fixed model approach within each subgroup (see Supplementary material online, Table S6). None of the HRs were statistically significant, except in the subgroup of patients with permanent AF in which an increased risk of hospitalization for HF was observed [HR 1.674, 95% CI (1.05–2.67)].

**Discussion**

**Main findings**

The main findings of this comprehensive meta-analysis of all randomized, placebo-controlled dronedarone trials were (i) There was a significant heterogeneity in treatment effects of dronedarone which persisted after careful adjustment for important baseline characteristics such as gender, LVEF, NYHA class, hypertension, previous stroke/TIA, history of coronary disease, and concomitant medical therapy. This heterogeneity dictated that a calculation of a single global treatment effect of dronedarone would not be
was the presence of permanent AF. On the other hand, patients of the drug on cardiovascular death (HR 2.319; 95% CI 1.13–4.75)

These subgroup analyses, the strongest predictor of a harmful effect or without CAD, and with or without permanent AF. According to these subgroup analyses, the strongest predictor of a harmful effect of the drug on cardiovascular death (HR 2.319; 95% CI 1.13–4.75) and hospitalization for heart failure (HR 1.674; 95% CI 1.05–2.67) was the presence of permanent AF. On the other hand, patients

The effects of dronedarone on cardiovascular outcomes in atrial fibrillation

This meta-analysis comprises data from 9664 individual patients who were enrolled in the placebo-controlled randomized clinical trials with this antiarrhythmic drug. All individual data were entered in a central database which allowed appropriate adjustments and subgroup analyses to be performed. This is in contrast to a previous meta-analysis based on published trial data and not on individual patient data.11

Three different endpoint events were analysed, cardiovascular death (218 patients) or cardiovascular hospitalization (1966 patients), the main contributor to the primary endpoint of ATHENA and PALLAS, and hospitalization for heart failure (377 patients) as the main driver of the harmful effect observed in ANDROMEDA and PALLAS. All fatal events had been blindly adjudicated as to the cause of death. For all three endpoints, there was significant heterogeneity across studies which excluded the calculation of an overall treatment effect of dronedarone. After careful adjustment for important baseline variables, significant heterogeneity persisted. We therefore performed analyses of four key subgroups, patients with or without digoxin therapy, with or without NYHA Class II or higher heart failure, with or without CAD, and with or without permanent AF. According to these subgroup analyses, the strongest predictor of a harmful effect of the drug on cardiovascular death (HR 2.319; 95% CI 1.13–4.75) and hospitalization for heart failure (HR 1.674; 95% CI 1.05–2.67) was the presence of permanent AF. On the other hand, patients

With digoxin

ANDROMEDA, ADONIS, ATHENA, PALLAS

0.087

No

2.153 (0.71–6.34)

Without digoxin

ANDROMEDA, ADONIS, ATHENA, PALLAS

0.281

No

0.758 (0.55–1.04)

Non-permanent AF

ANDROMEDA, ADONIS, ATHENA

0.042

Yes

NC

(0.41–3.03)

Permanent AF

ANDROMEDA, PALLAS

0.529

No

2.319 (1.13–4.75)

No CHF or NYHA

ANDONIS, ATHENA, PALLAS

0.367

No

0.836 (0.57–1.22)

NYHA II–IV

ANDROMEDA, ADONIS, ATHENA, PALLAS

0.005

Yes

NC

(0.60–3.07)

With CAD

ANDROMEDA, ADONIS, ATHENA, PALLAS

0.028

Yes

NC

(0.42–2.56)

Without CAD

ANDROMEDA, ADONIS, ATHENA, PALLAS

0.082

Yes

1.809 (0.67–4.91)

AF, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; NC, not calculated; NYHA, New York Heart Association; OAC, oral anticoagulants; TIA, transient ischaemic attack.

Significant P-value of interaction between study and treatment.

NC, not calculated—When the interaction P-value is significant, only the 95% CI of the HR calculated using the random-effect approach is provided.

Effects of dronedarone on cardiovascular outcomes in atrial fibrillation

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With non-permanent AF derived benefit from dronedarone with a significant reduction in cardiovascular hospitalization (HR 0.751; 95% CI 0.68–0.83).

Dronedarone in permanent vs. non-permanent atrial fibrillation

The striking finding of the PALLAS trial was that patients with permanent AF had increased cardiovascular mortality with dronedarone. Although the present analysis cannot provide a precise reason for this unexpected finding, it can be speculated that in permanent AF the beneficial effect of dronedarone on the maintenance of sinus rhythm was lost, while potential negative inotropic effects of the compound may have led to fatal heart failure episodes.

The heterogeneity of the treatment effects of dronedarone with respect to cardiovascular hospitalization was particularly high. The reason for this finding may be that in patients with non-permanent AF (ATHENA study) the number one reason for cardiovascular hospitalization was admission for management of AF, for instance cardioversion or adjustment of rate-controlling therapy. Dronedarone is quite good for preventing these types of hospitalization. In contrast, patients enrolled in ANDROMEDA or PALLAS were predominantly hospitalized for treatment of heart failure episodes, which were clearly increased by dronedarone. In ANDROMEDA and to a lesser extent in PALLAS, patients had more advanced cardiovascular disease and more comorbidities at enrolment than was seen in ATHENA patients.

Limitations

All meta-analyses have inherent limitations. Among those which also apply to our study is the classification of cardiovascular deaths. Although the same classification scheme was utilized in all dronedarone studies and although blinded evaluation committees were charged with this task, the possibility of occasional misclassification

Table 3 Cardiovascular death in selected subgroups after correction for important baseline covariates

<table>
<thead>
<tr>
<th>Included studies</th>
<th>Multivariate analysis interaction P-value</th>
<th>Interaction in Galbraith graphic</th>
<th>HR (95% CI)</th>
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<tr>
<td>With digoxin*</td>
<td>ANDROMEDA, ADONIS, ATHENA, PALLAS</td>
<td>0.087</td>
<td>No</td>
</tr>
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<td>Without digoxin*</td>
<td>ANDROMEDA, ADONIS, ATHENA, PALLAS</td>
<td>0.281</td>
<td>No</td>
</tr>
<tr>
<td>Non-permanent AF</td>
<td>ANDROMEDA, ADONIS, ATHENA</td>
<td>0.042*</td>
<td>Yes</td>
</tr>
<tr>
<td>Permanent AF</td>
<td>ANDROMEDA, PALLAS</td>
<td>0.529</td>
<td>No</td>
</tr>
<tr>
<td>No CHF or NYHA</td>
<td>ANDONIS, ATHENA, PALLAS</td>
<td>0.367</td>
<td>No</td>
</tr>
<tr>
<td>NYHA II–IV</td>
<td>ANDROMEDA, ADONIS, ATHENA, PALLAS</td>
<td>0.005*</td>
<td>Yes</td>
</tr>
<tr>
<td>With CAD</td>
<td>ANDROMEDA, ADONIS, ATHENA, PALLAS</td>
<td>0.028*</td>
<td>Yes</td>
</tr>
<tr>
<td>Without CAD</td>
<td>ANDROMEDA, ADONIS, ATHENA, PALLAS</td>
<td>0.082</td>
<td>Yes</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; NC, not calculated; NYHA, New York Heart Association; OAC, oral anticoagulants; TIA, transient ischaemic attack.

Significant P-value of interaction between study and treatment.

NC, not calculated—When the interaction P-value is significant, only the 95% CI of the HR calculated using the random-effect approach is provided.
cannot be excluded. Likewise, the diversity of patients enrolled in the various trials may lead to inherent difficulties. However, our analysis is based on individual patient data which is the most solid basis of any meta-analysis. In this respect, our analysis differs from a previous one. The early termination of two important dronedarone trials (ANDROMEDA and PALLAS) may cause bias due to the limited follow-up period available for individual patients. Finally, although the methodology used in this analysis did not fully eliminate the inter-study heterogeneity to calculate a global treatment effect, it did reduce it significantly thus allowing to draw useful conclusions on the treatment effect in two relevant subgroups of patients, those with and without permanent AF.

Conclusions
This meta-analysis based on individual patient data demonstrates significant heterogeneity of dronedarone treatment effects across the placebo-controlled randomized trials. The most important predictor of a harmful effect of dronedarone on cardiovascular death and heart failure hospitalization was the presence of permanent AF. For these patients, dronedarone is contraindicated.

Supplementary material
Supplementary material is available at Europace online.

Acknowledgements
The authors thank Dr Raphael Bejuit and Ms Valerie Corp-dit-Genti—Sanofi Recherche for their assistance with the biostatistical analyses.

Table 4  Cardiovascular hospitalization in selected subgroups after correction for important baseline covariates

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<tr>
<td>With digoxina&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DAFNE, ANDROMEDA, EURIDIS, ADONIS, ERATO, ATHENAS, PALLAS</td>
<td>0.402</td>
<td>No</td>
</tr>
<tr>
<td>Without digoxina&lt;sup&gt;a&lt;/sup&gt;</td>
<td>DAFNE, ANDROMEDA, EURIDIS, ADONIS, ATHENA</td>
<td>0.001&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>Non-permanent AF&lt;sup&gt;c&lt;/sup&gt;</td>
<td>DAFNE, ANDROMEDA, EURIDIS, ADONIS, ATHENA</td>
<td>0.269</td>
<td>Yes</td>
</tr>
<tr>
<td>Permanent AF&lt;sup&gt;d&lt;/sup&gt;</td>
<td>ANDROMEDA, ERATO, PALLAS</td>
<td>0.050&lt;sup&gt;b&lt;/sup&gt;</td>
<td>No</td>
</tr>
<tr>
<td>No CHF or NYHA&lt;sup&gt;e&lt;/sup&gt;</td>
<td>DAFNE, EURIDIS, ADONIS, ERATO, ATHENA, PALLAS</td>
<td>0.008&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Yes</td>
</tr>
<tr>
<td>NYHA II–IV&lt;sup&gt;f&lt;/sup&gt;</td>
<td>DAFNE, ANDROMEDA, EURIDIS, ADONIS, ERATO, ATHENA, PALLAS</td>
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<td>No</td>
</tr>
</tbody>
</table>

Baseline covariates entered into the model:
<sup>a</sup> AF status, NYHA, Creatinine clearance, LVEF, CAD, Diabetes, BB, Valvular heart disease, sex, ACE/ARB.
<sup>b</sup> NC: Not Calculated—When interaction P-value is significant, the 95% CI of the HR calculated using the random effect approach is provided.
<sup>c</sup> NYHA, Creatinine clearance, LVEF, CAD, diabetes, BB, Valvular heart disease, sex, OAC.
<sup>d</sup> AF status, Creatinine clearance, LVEF, CAD, diabetes, BB, Valvular heart disease, sex, OAC, diuretics.
<sup>e</sup> AF status, NYHA, Creatinine clearance, LVEF, CAD, diabetes, BB, Valvular heart disease, ACE/ARB, OAC, statins.
<sup>f</sup> ACE, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin II receptor blockers; BB, beta-blockers; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; NC, not calculated; NYHA, New York Heart Association; OAC, oral anticoagulants.

Conflict of interest: S.H.H. reports receiving consulting fees from Boehringer Ingelheim, St. Jude Medical, Sanofi-Aventis, Gilead, and Cardiome, and lecture fees from Boehringer Ingelheim, Bayer, Bristol-Myers Squibb, Pfizer, St. Jude Medical, Sanofi-Aventis, and Cardiome. S.J.C. reports receiving payment for serving on the boards of Boehringer Ingelheim, Sanofi-Aventis, Portola, and Pfizer, consulting fees from Boehringer Ingelheim, Sanofi-Aventis, Portola, and Merck, and grant support on behalf of his institution, McMaster University, from Boehringer Ingelheim, Sanofi-Aventis, Portola, and Bristol-Myers Squibb, and lecture fees from Boehringer Ingelheim, Sanofi-Aventis, and Portola. A.J.C. reports receiving payment for serving on the boards of Boehringer Ingelheim, Sanofi-Aventis, Novartis, Servier, consulting fees from Sanofi Aventis, Merck, J&J, Gilead, Daiichi, Bayer, and lecture fees from Sanofi Aventis. J.L.H. reports receiving payment for consulting fees from Sanofi-Aventis, Bayer, Boehringer Ingelheim, Daichi Sankyo, Janssen, Johnson & Johnson, Biotronik, Boston Scientific, Medtronic, and Pfizer. D.R. is an employee of Sanofi Aventis.

Funding
All studies on which the present meta-analysis is based upon were sponsored by Sanofi Aventis.

References


EP CASE EXPRESS

doi:10.1093/europace/eut344
Online publish-ahead-of-print 4 November 2013

Inappropriate implantable cardioverter-defibrillator shocks in a public swimming pool

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In a period of 1 year, three patients with an implantable cardioverter-defibrillator (ICD) presented to our outpatient clinic after receiving an ICD shock during a visit to one public swimming pool. Their electrograms showed high-frequency noise at a cycle length of 120 ms, well-matched with 50 Hz alternating current (Figure). We visited the pool with one patient and a team of engineers from our university. The noise was detectable in the water on the high-voltage electrodes near one of the exits. The signal became detectable on the pace/sense electrodes when the patient touched the handrails near this exit.

A grounding connection was present at the handrail. Measurements at the handrail indicated a relatively high leakage currents which was in total within normal limits, but concentrated on this earthing conductor creating a high local electric field. Protection against excessive leakage current is guaranteed by differential fuses, which open the electrical circuit above a predefined threshold. This has not occurred in before, confirming that leakage current was within the accepted limits. This is an example of potential environmental hazards to patients with an ICD. With the growing number of ICD patients, clinicians should be well aware of these environmental hazards and patients should be well informed to minimize these unnecessary risks.

The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/inappropriate-ICD-shocks.pdf.

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