Survival after withdrawal of dofetilide in patients with congestive heart failure and a short baseline QTc interval

A follow-up on the Diamond-CHF QT substudy

B. Brendorp\textsuperscript{a*}, C. Torp-Pedersen\textsuperscript{a}, H. Elming\textsuperscript{a}, L. Køber\textsuperscript{b}, for the DIAMOND study group

\textsuperscript{a}Department of Cardiology, Copenhagen University Hospital, Gentofte, Denmark
\textsuperscript{b}Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Denmark

Received 13 May 2002; accepted 26 June 2002

Background We have previously observed dofetilide to be associated with improved survival when the pre-treatment baseline QTc interval was below 429 ms. In this study we tested the natural extension of this observation—that the same group of patients should have a loss of survival benefit after withdrawal of dofetilide.

Methods Patients with congestive heart failure (CHF) and reduced left ventricular function enrolled in the Diamond–CHF (Danish Investigations of Arrhythmia and Mortality on Dofetilide–CHF) study were eligible for our QT substudy provided they were in sinus rhythm and had a measurable QTc interval from a 12-lead standard ECG taken before randomization to placebo or dofetilide. An extended follow-up was performed from study closure, December 1996 until August 2001.

Results Of the 418 patients entering the extended follow-up, 215 (51%) patients died during this 4.5 years of additional observation time. The baseline QTc interval made no prognostic difference to mortality in placebo treated patients. For dofetilide treated patients with a baseline QTc interval <7429 ms, increased mortality was observed during the extended follow-up compared to placebo (risk ratio 1.5, 95% confidence interval 1.1–2.8).

Conclusions This follow-up study shows significant loss of survival benefit upon withdrawal of dofetilide in patients with CHF and a pre-treatment QTc interval below 429 ms. An independent randomized trial is warranted to validate these results.

© 2003 The European Society of Cardiology. Published by Elsevier Science Ltd. All rights reserved.

KEYWORDS
QT interval; Heart failure; Prognosis; Antiarrhythmic agents

Introduction

Antiarrhythmic drugs have so far failed to improve survival in high risk patients.\textsuperscript{1–3} In the DIAMOND–CHF\textsuperscript{4} (Danish Investigations of Arrhythmia and Mortality on Dofetilide–Congestive Heart Failure) study, patients with CHF and left ventricular systolic dysfunction had a similar prognosis\textsuperscript{5} whether treated with the class III antiarrhythmic drug dofetilide\textsuperscript{6} or placebo. A prospective substudy of this trial, the Diamond–CHF QT substudy, comprised all patients from the main trial in sinus rhythm with a measurable QTc interval. In these patients, a pre-treatment (baseline) QTc interval below 429 ms was associated with a significant 60% reduction in mortality for patients subsequently...
treated with dofetilide compared to placebo, with increasing risk of mortality as baseline QTc intervals increased.7

This led to the hypothesis that for ‘pure’ class III antiarrhythmic drugs, the baseline QTc interval should be used to identify patients who would benefit from treatment in regards to mortality.7 This hypothesis remains to be validated in an independent prospective clinical trial.

If the hypothesis is correct then a loss of survival benefit should be expected upon withdrawal of the drug. In this study we have tested this supposition by examining the relation between initial pre-treatment QTc measurement and long-term survival following withdrawal of dofetilide.

Methods

The Diamond–CHF study population

Patients enrolled in the Diamond–CHF study4 fulfilled the inclusion criteria of age ≥18 years, NYHA functional class III or IV within the last month, hospitalization with CHF, and a wall motion index (WMI) of the left ventricle ≤1.2 (corresponding to an ejection fraction ≤35%) estimated by echocardiography. Fifteen hundred and eighteen patients were double-blindly randomized to placebo or dofetilide.

Exclusion criteria4 included patients with a locally measured baseline QTc interval (single lead measurements, available in all patients) exceeding 460 ms (500 ms if bundle-branch block). A written informed consent was given by all participants, and the study was approved by the Danish Board of Health and the involved ethics committees.

The Diamond–CHF QT substudy

The Diamond–CHF QT substudy, a prospective substudy based on the Diamond–CHF study population, investigated the prognostic value of the pre-treatment QTc interval7 in CHF patients in sinus rhythm randomized in the Diamond CHF study.

A pre-treatment ECG of 1319 of the 1518 patients was sent for central evaluation in our department. As previously described,7 an all-lead averaged QTc interval measurement was performed in each of the 1319 ECGs by one of two experienced observers using a computerized digitiser tablet. Due to exclusion criteria (atrial fibrillation, <9 readable leads, poor recording quality, pacemaker rhythm, and bigeminy) acceptable QTc interval measurements were only available in 630 patients with genuine baseline ECGs, and in 73 placebo-treated patients without baseline ECGs, but with an ECG taken within 6 days after randomization. Thus 703 patients entered the substudy. Follow-up was a minimum of 1 year (median follow-up 18 months).7

Follow-up on the Diamond–CHF QT substudy

After withdrawal of study treatment at study closure on 6 December 1996, an extended follow-up on mortality status of all patients included in the Diamond–CHF QT substudy was performed in all patients on 3 August 2001. No patients were lost to follow up. ECG measurements from the Diamond–CHF QT substudy were used for this study. The primary endpoint was all-cause mortality.

Statistical analysis

The statistical software used was SAS version 8.0. Baseline comparison was performed by non-parametric analysis of variance and by chi-square tests. Continuous data are reported as median and 5/95% percentiles. Survival analysis consisted of Kaplan–Meier curves and estimates, and univariate and multivariate Cox proportional hazard models, performed on an intention-to-treat basis. The covariates chosen for the extended follow-up model were the same as for the original substudy follow-up model7 in order for the QTc interval results in the two models to be comparable. Likewise, the grouping of the baseline QTc intervals in quartiles was repeated in the extended follow-up model. Assumptions of the Cox model were successfully verified. The results of the Cox analysis are reported as risk ratios (RR), with a 95% confidence interval. The level of significance was set at 0.05.

Results

Baseline characteristics and mortality

Two hundred and thirty-four placebo- and 184 dofetilide-treated patients entered the extended follow-up. Baseline characteristics are shown in Table 1. There was no significant difference in baseline variables between placebo- and dofetilide-treated patients.

Comparing baseline variables for the 418 patients entering the extended follow-up with the rest of the 1518 patients entering the main Diamond–CHF study showed that patients entering the extended follow-up were younger (69 vs 72 years), had a shorter history of CHF (5 vs 13 months), were less often in NYHA class 3 or 4 (55 vs
62%), and less often had a history of diabetes (15 vs 21%). They less often received digoxin at randomization (48 vs 68%), and more often beta-blockers (13 vs 9%). The baseline QTc interval (and QT dispersion) was similar in the two study populations, but patients entering the extended follow-up had a lower baseline heart rate (78 vs 82 beats min⁻¹).

One-hundred and twenty-three placebo- (53%) and 92 dofetilide-treated (50%) patients died during the extended follow-up (Table 2).

**Univariate survival analysis**

Patients in the lowest baseline QTc interval quartile (<29 ms) had a non-significant 35% increase in mortality risk in the dofetilide group (RR 1.35, 95% CI 0.8–2.2, P=0.2) compared to placebo.

Cumulative mortality curves for dofetilide-treated patients confirmed a reversal in the relationship between mortality and baseline QTc intervals for the two follow-up periods when comparing the lowest baseline QTc interval quartile (<429 ms) against the other three quartiles (Fig. 1).

For placebo-treated patients, no relationship was found between mortality and QTc interval quartiles (log-rank test: P>0.9).

**Multivariate survival analysis**

The baseline QTc interval in the dofetilide group was divided up into quartiles and (as pre-defined)
compared to the placebo group as a whole (with a default RR of 1, as there was no prognostic value of the baseline QTc interval in the placebo group) in multivariate survival analysis. The results from this model showed a significant effect on mortality for dofetilide-treated patients in the lowest baseline QTc interval quartile (Table 3). Using the lowest QTc interval quartile in the placebo group as a reference, results were similar, but statistically non-significant (RR: 1.4, 0.7, 0.8, 0.8; P-values 0.18, 0.14, 0.43, 0.47).

No significant interaction between the variable for placebo/dofetilide and the baseline QTc interval was found for the extended follow-up (P>0.1). For 282 of the 418 patients entering the extended follow-up, a post-randomization QTc interval was available from an ECG taken within 2 to 6 days after randomization. Although the QTc interval was prolonged in the dofetilide group (26(-22/86) ms) compared to placebo (27(-45/29) ms), no significant interaction was found between the baseline QTc interval and post-randomization changes in the QTc...
interval regarding mortality ($P$ value for interaction between the baseline QTc interval and post-randomization QTc interval changes: dofetilide $P<0.8$, placebo $P=0.1$).

In subgroup analysis performed to seek any difference in the prognostic value of the baseline QTc interval in dofetilide treated patients for baseline variables, no significant interaction was found. Investigators’ single-lead measurements showed similar, but much weaker results than our multiple-lead measurements (placebo: no prognostic value; dofetilide: RR: 1.2, 1.0, 0.8, 1.0; $P$-values: 0.21, 0.81, 0.15, 0.80).

### Discussion

This study demonstrates that the survival benefit of dofetilide in patients with congestive heart failure and a short baseline QTc is lost following discontinuation of therapy. Thus, the study strengthens the hypothesis that dofetilide increases survival for these patients.

During the original study period for the Diamond–CHF QT substudy, 42% of placebo-treated and 39% of dofetilide-treated patients died. Univariate survival analysis showed a significant 50% reduction in mortality risk in the dofetilide group compared to placebo when the baseline QTc interval was $<429$ ms (risk ratio 0.5, 95% CI 0.3–0.9, $P<0.02$). Multivariate analysis confirmed this effect with no prognostic value for the placebo group, and a steady increase in the mortality risk ratio with longer baseline QTc intervals (divided into quartiles according to the baseline QTc interval) in the dofetilide group. The latter provided a significantly reduced mortality risk compared to placebo when the baseline QTc interval was below 429 ms, and a non-significantly increased risk when the baseline QTc interval was above 454 ms (QTc interval $<429$ ms: risk ratio 0.4, 95% CI 0.3–0.8, $P<0.005$, QTc interval 429–454 ms: 0.8 (0.5–1.2), $P<0.26$, QTc interval 454–479 ms: 1.1 (0.7–1.7), $P<0.82$, QTc interval $>479$ ms: 1.3 (0.8–1.9), $P=0.30$).7

In this study, survivors of the original substudy showed a significant loss of survival benefit after withdrawal of dofetilide. The study does not explain why, but it most likely lies in the effect on ventricular repolarization. If this is so, the beneficial effect of antiarrhythmic treatment in this case has outweighed the risk of proarrhythmia known to be associated with antiarrhythmic drugs.

A prolonged baseline QTc interval is a well-established contraindication for antiarrhythmic treatment with drugs that further prolong repolarization.8 Also, if a patient on treatment has an excessive QTc interval increase, this usually leads to withdrawal of the drug in order to avoid proarrhythmias, primarily torsade de pointes ventricular tachycardia. If the hypothesis generated from the current study is proven valid in an independent prospective clinical trial, the consequence will be that QTc interval measurement of all available leads will be a key selection criterion when choosing patients for treatment with dofetilide and possibly other class III antiarrhythmic drugs. As with other drugs of this class, dofetilide can only reduce the risk of serious ventricular arrhythmia if the benefit of an increase in the refractory period is not outweighed by an increase in proarrhythmia due to excessive prolongation of the refractory period. If, as suggested by the results of our previous study,7 such a group of patients have been identified, it is expected that the shortening of the refractory period after discontinuing the drug be accompanied by an increase in the risk of ventricular arrhythmias. We have no ECGs to show such a shortening of the refractory period after dofetilide discontinuance, but a reversal in mortality risk from benefit to increased risk of mortality after dofetilide discontinuance, as shown in the present study, suggests such a mechanism.

Measurement of the QTc interval appears simple but in fact covers a wide range of different techniques, which each give different results. This should be kept in mind when comparing studies both in terms of absolute values and in terms of survival data. In a recent policy report on QT prolongation with non-antiarrhythmic drugs,9 the use of multiple leads rather than single-lead measurements (usually lead II) was favoured, as the distribution of maximal and minimal QT intervals throughout a 12-lead ECG is not stable. Our results support this recommendation, since our multiple-leads measurements yielded more distinct results than those from the single-lead measurements made by the local investigators.

### Conclusion

In conclusion, this follow-up study shows a significant loss of survival benefit upon withdrawal of dofetilide in patients with CHF, reduced left ventricular systolic function, and a pre-treatment QTc interval below 429 ms. An independent randomized trial is warranted to validate these results.

### Study limitations

The results of this follow-up should be interpreted with caution for the following reasons. The study
was retrospective and based on a substudy. The number of patients included was relatively low. Treatment strategies have changed. Patients with a baseline QTc interval (single-lead measurement) above 460 ms (above 500 ms in the case of bundle branch block) were not included in this study because of the exclusion criteria of the main Diamond–CHF study.

Acknowledgement
This study was supported by a grant from the Danish Heart Association.

References