QTc Interval as a Guide to Select Those Patients With Congestive Heart Failure and Reduced Left Ventricular Systolic Function Who Will Benefit From Antiarrhythmic Treatment With Dofetilide

Bente Brendorp, MD; Hanne Elming, MD, PhD; Li Jun, MD; Lars Køber, MD, DMSc; Marek Malik, MD, PhD, DMSc; Gorm Boje Jensen, MD, DMSc; Christian Torp-Pedersen, MD, DMSc; for the DIAMOND Study Group

Background—A prolonged QTc interval is considered a contraindication for class III antiarrhythmic drugs, but the influence of a normal or a slightly increased baseline QTc interval on the risk or benefit of treatment with a class III antiarrhythmic drug is not sufficiently clarified.

Methods and Results—This prospectively defined substudy included 703 patients enrolled in the Danish Investigations of Arrhythmia and Mortality on Dofetilide-Congestive Heart Failure (DIAMOND-CHF) study. Patients included had moderate to severe CHF and reduced left ventricular systolic function. Baseline QTc interval was measured before randomization to either dofetilide, a new class III antiarrhythmic drug, or placebo. During a median follow-up of 18 months (minimum 1 year), 285 patients (41%) died. Baseline QTc interval had no prognostic value on survival in placebo-treated patients. In dofetilide-treated patients, a baseline QTc interval, 429 ms was associated with a significant risk reduction (risk ratio 0.4, 95% CI 0.3 to 0.8). With increasing QTc interval, the risk increased gradually, and for QTc interval >479 ms, risk ratio was 1.3 (0.8 to 1.9).

Conclusions—A baseline QTc interval within normal limits is associated with a marked reduction of mortality in patients with CHF and left ventricular systolic dysfunction treated with dofetilide. This is a potentially important indication of which patients with CHF might benefit from prophylactic treatment with an antiarrhythmic drug. (Circulation. 2001; 103:1422-1427.)

Key Words: heart failure ■ prognosis ■ antiarrhythmia agents
TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=402, 57%)</th>
<th>Dofetilide (n=301, 43%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (perc)</td>
<td>70 (51–84)</td>
<td>70 (49–82)</td>
<td>*</td>
</tr>
<tr>
<td>Male sex, % (n)</td>
<td>73 (295)</td>
<td>69 (208)</td>
<td></td>
</tr>
<tr>
<td>Duration of heart failure, mo (perc)</td>
<td>12 (0.07–144)</td>
<td>12 (0.07–108)</td>
<td>*</td>
</tr>
<tr>
<td>Current smoker, % (n)</td>
<td>36 (146)</td>
<td>34 (102)</td>
<td>*</td>
</tr>
<tr>
<td>Medical history, % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>55 (222)</td>
<td>55 (165)</td>
<td>*</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>72 (291)</td>
<td>70 (210)</td>
<td>*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17 (69)</td>
<td>19 (57)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (60)</td>
<td>14 (42)</td>
<td></td>
</tr>
<tr>
<td>WMI (perc)</td>
<td>0.9 (0.5–1.2)</td>
<td>0.9 (0.5–1.2)</td>
<td></td>
</tr>
<tr>
<td>NYHA functional class III or IV, % (n)</td>
<td>56 (221)</td>
<td>63 (189)</td>
<td>0.04</td>
</tr>
<tr>
<td>Serum potassium, mmol/L (perc)</td>
<td>4.3 (3.7–5.1)</td>
<td>4.4 (3.5–5.2)</td>
<td>*</td>
</tr>
<tr>
<td>Serum creatinine, mmol/L (perc)</td>
<td>112 (82–185)</td>
<td>110 (80–183)</td>
<td>*</td>
</tr>
<tr>
<td>Medications at randomization, % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>11 (45)</td>
<td>12 (35)</td>
<td>*</td>
</tr>
<tr>
<td>Digoxin</td>
<td>50 (199)</td>
<td>56 (168)</td>
<td>0.10</td>
</tr>
<tr>
<td>Diuretics</td>
<td>96 (384)</td>
<td>95 (287)</td>
<td>*</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>77 (309)</td>
<td>76 (228)</td>
<td>*</td>
</tr>
<tr>
<td>ECG at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS ≥120 ms, % (n)</td>
<td>38 (153)</td>
<td>41 (122)</td>
<td>*</td>
</tr>
<tr>
<td>QT interval, ms (perc)</td>
<td>395 (335–472)</td>
<td>393 (319–472)</td>
<td>*</td>
</tr>
<tr>
<td>QTc interval, ms (perc)</td>
<td>454 (398–518)</td>
<td>454 (402–512)</td>
<td>*</td>
</tr>
<tr>
<td>Heart rate, bpm (perc)</td>
<td>79 (57–105)</td>
<td>80 (58–109)</td>
<td></td>
</tr>
</tbody>
</table>

All continuous variables are reported by median and 5%–95% percentiles (perc).

*P value >0.1.

Methods

Patients

The Diamond-CHF study was a double-blind, placebo-controlled, randomized study prospectively evaluating the effect of dofetilide on mortality for patients with CHF. The study was conducted in 34 hospitals in Denmark from 1993 to 1996. Patients were screened consecutively if they fulfilled the following criteria: age ≥18 years and hospitalization with CHF of all causes with an NYHA functional class III or IV within the last month before randomization. The screening procedure included echocardiography, and to be randomized, the patients were required to have left ventricular systolic dysfunction with a wall motion index (WMI) ≤1.2, corresponding to an ejection fraction ≤35. Of the 5812 patient screenings, 1518 patients were enrolled.

In accordance with the main study protocol, a 12-lead baseline ECG was available locally in all 1518 patients enrolled. Our predefined substudy protocol required that an additional predose baseline ECG was sent to us for central evaluation, and this was achieved in 1319 patients. All definitions were made before QT data were compared with survival data.

Patients with an acute myocardial infarction within 7 days, a locally measured baseline QTc interval >460 ms (500 ms in patients with bundle-branch block [BBB]), severe noncardiac disease, severe electrolyte abnormality, or severe renal dysfunction and patients receiving a class I or class III antiarrhythmic drug were excluded. Patients unwilling to participate or incapable of participation were also excluded.

Written informed consent was obtained. The study was approved by the Danish Board of Health and the involved ethics committees.

QTc Interval

QT interval was measured in 630 ECGs (48%) of the 1319 baseline ECGs recorded. Reasons for not measuring QT interval were atrial fibrillation (n=371), <9 readable leads (n=259), poor recording quality (n=11), pacemaker rhythm (n=45), and bigeminy (n=3). Another 73 ECGs of placebo-treated patients without baseline ECG but with a measurable ECG taken within 6 days after randomization were included in the study, leading to 703 patients with a measurable ECG.

Two consecutive QT intervals were measured in all 12 leads of a standard ECG by 1 of 2 experienced observers by a computerized digitizer tablet (Cherry, Mk III Graphic tablet, resolution 0.1 mm). The QT interval was measured from the beginning of the QRS complex to the visual return of the T wave to the isoelectric line and was heart rate–corrected with the Bazett formula, QTc = QT/√RR (resulting in a Pearson correlation coefficient between heart rate and QTc interval of 0.11 compared with a Pearson correlation coefficient between heart rate and the uncorrected QT interval of −0.73). A mean QTc interval was calculated from all QTc intervals measured. This method is similar to several other relevant studies. When the T wave was interrupted by a U wave, the end of the T wave was defined as the nadir between the T and the U wave. When the nadir was not defined, the lead was discarded from analysis.

Follow-Up

Patients were followed up for a minimum of 1 year (median follow-up 18 months). No patient was lost to follow-up.

End Points

End points were mortality end points from the main DIAMOND-CHF study. The primary end point was all-cause mortality, and secondary end points included death from cardiac causes as evalu-

TABLE 2. Baseline ECG Characteristics in Survivors and Nonsurvivors for Placebo- and Dofetilide-Treated Patients

<table>
<thead>
<tr>
<th>Baseline ECG</th>
<th>Placebo Survivors (n=234)</th>
<th>Placebo Nonsurvivors (n=168)</th>
<th>P1</th>
<th>Dofetilide Survivors (n=184)</th>
<th>Dofetilide Nonsurvivors (n=117)</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>QT interval, ms</td>
<td>400 (335–478)</td>
<td>391 (336–460)</td>
<td>0.06</td>
<td>390 (318–476)</td>
<td>396 (319–469)</td>
<td>0.70</td>
</tr>
<tr>
<td>QTc interval, ms</td>
<td>453 (400–519)</td>
<td>454 (396–507)</td>
<td>0.59</td>
<td>450 (396–506)</td>
<td>465 (403–518)</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>77 (57–108)</td>
<td>82 (59–102)</td>
<td>0.14</td>
<td>79 (57–109)</td>
<td>82 (62–109)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Continuous variables reported as median and 5%–95% percentiles. P denotes differences between survivors and nonsurvivors in placebo-treated patients; P2 denotes differences for dofetilide-treated patients.
ated by members of an event committee of the main study. All available data in connection with an end point were reviewed on a blinded basis, and the end point was subsequently classified according to the CAPS criteria (with the exception that successful resuscitation of cardiac arrest was not considered as death).

Statistical Analysis
Continuous data are reported as median and 5%/95% percentiles. Comparisons between groups were made by χ² test for discrete data and by nonparametric ANOVA (Kruskal-Wallis test) for continuous data.

Survival analysis included Kaplan-Meier curves and univariate and multivariate Cox proportional-hazard models. Variables considered for multivariate analysis were QTc interval; placebo/dofetilide; sex; age; heart rate; smoking status; history of diabetes, ischemic heart disease, or hypertension; use of β-blockers, calcium antagonists, digoxin, or diuretics; BBB; WMI; NYHA class; and serum potassium and creatinine. Only variables with independent prognostic importance were retained in the final model. Assumptions of the Cox models (proportional hazards, interactions, and linearity for the risk estimates of a continuous variable) were tested. QTc interval and QTc prolongation between baseline and day 2 to 6 were tested both as continuous variables and as quartiles (the latter analysis being used for the final model). Results from the Cox analysis are expressed as relative risk (RR) with a 95% CI.

The Statistical Analysis System version 6.12 (SAS Institute, Inc) was used for all statistical analysis. Analysis was made on an intention-to-treat basis. A test was considered statistically significant at a corresponding value of P=0.05.

Results
Baseline Characteristics and QTc Interval
Table 1 shows baseline characteristics in the placebo group and in the dofetilide group. QTc intervals were longer for patients with BBB (QRS ≥120 ms) in both groups (placebo group, 473 [416 to 532] versus 442 [394 to 494] ms; dofetilide group, 475 [426 to 515] versus 443 [390 to 500] ms). For patients with ischemic heart disease and for patients treated with digoxin, there was a tendency toward shorter QTc intervals. There was no difference in QTc interval between groups with or without treatment with β-blockers, diuretics, or ACE inhibitors.

End Points and QTc Interval
During follow-up, 168 placebo-treated patients (42%) and 117 dofetilide-treated patients (39%) died. Of these, 125 (31%) and 94 (31%) patients died of cardiac causes, respec-

tively. Table 2 shows QT parameters for survivors and nonsurvivors in the 2 treatment groups.

Univariate Survival Analysis
All-cause mortality curves for placebo- and dofetilide-treated patients are shown in Figure 1. Similar results were also seen for cardiac death (log-rank test, placebo group, P>0.7; log-rank test, dofetilide group, P<0.02).

Considering only patients from the 2 lower QTc interval quartiles, patients receiving dofetilide had an all-cause mortality risk reduction of 40% compared with the placebo group (risk ratio 0.6, 95% CI 0.4 to 0.9, P<0.02). For the 2 upper QTc interval quartiles, dofetilide demonstrated a trend for a 20% increased mortality risk compared with placebo (1.2, 0.9 to 1.7, P>0.16).

Multivariate Survival Analysis
A considerable difference in the effect of QTc interval on mortality between placebo- and dofetilide-treated patients was confirmed in the test for interaction (P=0.0004), making it necessary to consider placebo- and dofetilide-treated patients separately.

The variable for QTc interval was then divided into quartiles in multivariate analysis to substantiate the difference between placebo- and dofetilide-treated patients, with the lowest quartile for placebo-treated patients serving as reference (with a default risk ratio of 1) for both treatment groups.

Table 3 and Figure 2 show the results from multivariate Cox analysis for all-cause mortality. A similar analysis on maximum QTc interval revealed a similar but weaker tendency on all-cause mortality.

BBB did not hold multivariate predictive value for all-cause mortality in either of the 2 treatment groups (placebo, P>0.7; dofetilide, P>0.3). In the dofetilide group, QTc interval contained greater predictive value for patients without BBB than those with BBB (test for interaction, P=0.03). No such tendency was seen in the placebo group.

To test whether the prognostic value of QTc interval was carried solely by the effect of heart rate included in the QTc interval, analysis was repeated after QTc interval was replaced with heart rate. No difference in prognostic value was seen between placebo- and dofetilide-treated patients (test for interaction, P=0.27). Also, in a model in which the uncorrected QT interval and heart rate were included as separate
variables, QT interval contained independent prognostic value as long as heart rate was retained in the analysis.

In 454 of the 703 patients, QTc interval was available from an ECG taken within 2 to 6 days after randomization. For dofetilide-treated patients, QTc interval increment from baseline to day 2 to 6 was larger for the lower quartiles (median differences [in ms], lower to upper quartiles: 32 [26–4/94], 33 [1/82], 23 [22–9/79], 15 [23–2/62], \( P = 0.0002 \)). Multivariate survival analysis on postrandomization ECGs showed the same tendency (but weaker) for the effect of QTc interval quartiles on mortality in the dofetilide group as for analysis made on baseline ECGs. Interaction analysis revealed no relationship on all-cause mortality between baseline QTc interval and changes in QTc intervals from baseline to day 2 to 6 (\( P = 0.17 \)).

For patients who suffered a cardiac death, a weaker but similar tendency in the prognostic value of the QTc interval was seen as for patients who died from all-cause mortality (placebo: no prognostic value; dofetilide: RR 0.5, 0.9, 1.2, 1.3; probability value 0.04, 0.78, 0.58, 0.27).

In the dofetilide-treated patients, the prognostic importance of the QTc interval was not dependent on stratification by sex (\( P = 0.27 \), with probability value referring to test for interaction between QTc interval and stratum), age (<60 years, ≥60 years) (\( P = 0.62 \), WMI (<1, 1 to 2) (\( P = 0.96 \)), smoking status (\( P = 0.40 \), serum creatinine (≥130 mmol/L, >130 mmol/L) (\( P = 0.98 \)), NYHA class (I and II, III and IV) (\( P = 0.57 \)), diabetes (\( P = 0.47 \), ischemic heart disease (\( P = 0.78 \), arterial hypertension (\( P = 0.16 \), β-blocker (\( P = 0.48 \), or digoxin (\( P = 0.94 \)).

Analysis on the locally measured baseline QTc interval (single-lead measurements, preferably in lead II, by an investigator at the local site just before randomization) on all-cause mortality for all patients randomized revealed the same trend as for our measurements, although this did not reach statistical significance (placebo: no prognostic value; dofetilide: RR 0.8, 0.9, 1.0, 1.03; probability value 0.10, 0.53, 0.98, 0.83).

The above-mentioned results of our study were tested excluding the 73 placebo-treated patients with postrandomization ECGs only. This did not change the results.

### Discussion

This study suggests that dofetilide reduces mortality in patients with CHF and reduced left ventricular systolic function, provided that QTc interval before treatment is short. For those patients within the highest quartile of baseline QTc interval, the risk of death is increased compared with placebo, albeit not significantly. The median QTc in our study was 454 ms, close to the upper normal limit of 440 ms used in many studies.

Our data do not explain the findings, but a likely explanation may lie in the balance between the protective effect of prolonging the refractory period with class III antiarrhythmic...
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effect of outliers. It is therefore not surprising that a more

precise result is obtained in this much smaller study. The

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tage of being biased by measurement errors. It is therefore not

surprising that similar but insignificant trends were obtained

with maximal QTc intervals compared with mean QTc

intervals in our study.

No other study has addressed the issue reported in this

article. The prognostic value of QTc interval in patients

with CHF is likewise poorly described in the literature. The only

larger prospective multivariate survival study on QTc interval

for patients with CHF so far was made by Brooksby et al.11

During a mean (SD) follow-up of 471 (168) days, 71 (14%)
of the 554 patients died. Maximum QTc interval was found to

hold no multivariate prognostic value on all-cause mortality

(RR and CI not supplied). In 603 post–myocardial infarction

patients with CHF, Spargias et al6 found QTc interval in

nonsurvivors to be longer than in survivors (nonsurvivors,

mean [SD] QTc interval 447.2 [40.2]; survivors, 431.8 [33.4],

P<0.001), but multivariate survival analysis was not per-
formed on QTc interval. Small-scale studies on differences in

QTc interval for survivors and nonsurvivors in CHF patients

are variably negative7,12–14 and positive.15

Baseline QTc interval prolongation is known to be a cause

for caution when prescribing class Ia or class III antiarryth-
mic drugs, because they may induce TdP VT.1 Our study

raises the intriguing question of whether other, mostly neu-

tral16 or negative17 prognostic studies regarding prophylactic

use of class III antiarrhythmic drugs in high-risk patients

could have had a different outcome had the patients been

stratified according to baseline QTc intervals. Perhaps an

insufficient risk stratification of the patients rather than lack

of efficacy of the drugs caused the results of these studies. In

this context, it is important to note that investigator measure-
ment in a single lead only indicated a trend, compared with

the much more convincing result of a measurement based on

all available leads. Therefore, future studies and reevaluation

of previous studies should attempt to use measurements based

on multiple leads.

Study Limitations

The most important limitation is that the data come from a

substudy of a randomized clinical trial with a neutral out-
come. Therefore, the results must be interpreted with caution

and need to be confirmed in other studies as well as in a

prospective clinical trial before they can be considered fully

valid.

As a result of the combined entry criteria of NYHA class

III/IV and low left ventricular systolic function, this study

was performed on high-risk CHF patients. This was before

the use of β-blockers and spironolactone was implemented

in patients with CHF. Therefore, our results cannot be directly

applied to all CHF patients treated with present treatment

strategies.

One of the exclusion criteria for the DIAMOND-CHF

study was a QTc (single lead) >460 ms (>500 ms in case of

BBB). This may have excluded some patients with repolar-

ization abnormalities from our study.

Conclusions

In dofetilide-treated patients with moderate to severe CHF

and reduced left ventricular systolic function, a short baseline

QTc interval is associated with reduced mortality. With

increasing baseline QTc interval, the risk of death systemat-
cally increases. Our study is the first to point to a possible

risk stratification strategy from a standard ECG in high-risk

CHF patients with respect to subsequent treatment with a

class III antiarrhythmic drug.

Acknowledgment

The DIAMOND study was supported by a grant from Pfizer.

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