Individual Patterns of Dynamic QT/RR Relationship in Survivors of Acute Myocardial Infarction and Their Relationship to Antiarrhythmic Efficacy of Amiodarone

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Postinfarction QT/RR Dynamics. ***Introduction:*** **Amiodarone is an effective antiarrhythmic drug, but it has serious side effects and conducted trials did not support its prophylactic use in survivors of acute myocardial infarction. It is possible that the prophylactic use of the drug has not been tested effectively. To optimize therapy outcome, markers of drug efficacy might be developed to identify patients who, although at arrhythmic risk, would not benefit from amiodarone treatment. We investigated descriptors of QT/RR relationship for their potential value in predicting inefficient amiodarone treatment.**

Methods and Results: **The study used 866 Holter recordings (462 amiodarone, 404 placebo) obtained 1 month after randomization in the European Myocardial Infarct Amiodarone Trial (EMIAT). A commercial Holter system was used to measure RR and QT intervals. Subject-specific descriptors of QT/RR relationship were calculated. Comparison was performed in amiodarone- and placebo-treated patients, distinguishing patients who did and did not suffer from arrhythmic death. QT/RR relationship and individually corrected QTc interval differed significantly, not only between amiodarone- and placebo-treated postmyocardial infarction patients but also between patients with and without arrhythmic death on amiodarone (QTc with vs without arrhythmic death 426.30 $\pm$ 33.93 ms vs 444.23 $\pm$ 36.65 ms, $P = 6.5 \times 10^{-3}$). In a multivariate analysis, reduced optimum regression residuum (14.33 $\pm$ 7.08 vs 20.11 $\pm$ 9.39, $P = 4.4 \times 10^{-3}$) and flatter slope (0.44 $\pm$ 0.19 vs 0.55 $\pm$ 0.24, $P = 4.0 \times 10^{-2}$) of the QT/RR relationship independently predicted arrhythmic death during follow-up.**

Conclusion: **Chronic amiodarone treatment markedly affects the QT/RR relationship. The lack of treatment-related QT/RR changes predicts arrhythmic death. Descriptors of complexity of QT/RR relation seem to be potent markers of treatment efficiency.** *(J Cardiovasc Electrophysiol, Vol. 15, pp. 1147-1154, October 2004)*

antiarrhythmic agents, repolarization, heart rate, sudden death

Introduction

The efficacy of amiodarone in the treatment of ventricular arrhythmias has been reported repeatedly.[1] However, in both European Myocardial Infarct Amiodarone Trial (EMIAT)[2] and Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT),[3] amiodarone only reduced arrhythmic mortality; it failed to improve overall survival. The lack of overall prophylactic effect and the risk of serious adverse side effects of chronic amiodarone treatment led to the conclusion that implantable defibrillators are presently the only prophylactic antiarrhythmic option in patients surviving acute myocardial infarction. It is possible, however, that the amiodarone trials used enrollment criteria that were too broad and that markers of arrhythmic risk could improve patient selection. Shortly after treatment initiation, tests of amiodarone efficacy may allow identification of subjects who, although at arrhythmic risk, would not benefit from the treatment. A substudy of EMIAT showed that depressed heart rate variability identifies postinfarction patients who, due to their high arrhythmic risk, might benefit from prophylactic amiodarone treatment.[4] Studies of markers of amiodarone's therapeutic efficacy are inconsistent.

In clinical practice, serum levels of amiodarone and its metabolite desethylamiodarone are often used to assess drug efficacy. However, serum levels do not predict recurrence of ventricular arrhythmias.[5] Use of programmed electrical stimulation was suggested to estimate the efficacy of amiodarone treatment,[6] but other reports disagreed.[7] The value of suppression of ventricular arrhythmias on Holter recordings in predicting efficacy remains controversial,[8,9] and no consensus regarding the use of prolongation of heart rate Bazett-corrected QT interval as a marker of drug efficacy exists.[5,10]

The QT/RR relationship is altered after myocardial infarction,[11] and impaired adaptation of repolarization to heart rate changes increases arrhythmic risk.[12,13] The antiarrhythmic efficacy of amiodarone was partly explained by modulation of repolarization/rate adaptation, i.e., by an almost heart rate independent prolongation of the QT

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interval.[14,15] We hypothesized that if the reduction of arrhythmic mortality by amiodarone is related to modification of QT interval/heart rate adaptation, the extent of change in QT/RR relationship can be used as a marker of therapeutic efficacy.

This study investigated the QT/RR relationship and individually heart rate-corrected QT (QTc) intervals in amiodarone- and placebo-treated survivors of acute myocardial infarction in relation to arrhythmic death during follow-up.

Methods

Study Population

The study used data collected during a 1-month follow up of EMIAT.[2] Eligible patients were survivors of acute myocardial infarction aged 18 to 75 years who had left ventricular ejection fraction $\leq$40% assessed by multiple-gated nuclear angiography between days 5 and 21 after the index infarction. A total of 866 24-hour three-channel Holter recordings (462 on amiodarone, 404 on placebo) was obtained 1 month after treatment randomization. All of the recordings were available for this study. Clinical characteristics of study population are listed in Table 1.

Data Preparation

A commercial Holter system (Pathfinder, Reynolds Medical Inc., Hertford, UK) was used to measure RR and QT intervals in the 24-hour Holter recordings automatically on a beat-to-beat basis. Analysis was performed under careful visual control with manual artifact elimination. In each Holter lead, only beats with accepted QT and RR intervals were considered. In each recording, the lead with most accepted measurements was selected for further analysis.

The lag of QT/RR hysteresis was investigated in each recording by considering weighted averages $\overline{RR}$ of RR intervals in a window preceding each beat (see Appendix for technical details). In each patient, we identified the optimum averaging window of QT/RR hysteresis that led to the minimum global residuum of QT/$\overline{RR}$ regression using 10 regression models from an *a priori* defined set of regression equations. The regression models[16] were designed to cover a physiologic variety of QT/RR patterns because the patterns differ significantly between subjects.[16] Using a technology described in the Appendix, optimum weighting function was obtained for each recording to describe the dependency of QT interval on the history of preceding RR intervals. For each cardiac beat with valid QT interval, the weighting function was used to derive the corresponding numerical representation of RR interval history. For each QT interval measurement, the $\overline{RR}$ interval value was obtained in this way. The regression model leading to the smallest QT/$\overline{RR}$ residuum subsequently was selected and used to calculate the individually optimized QTc values through the whole recording.

Statistical Analysis

For each Holter recording:

- QT intervals were averaged over 10-ms $\overline{RR}$ interval bins from 550 to 1,150 ms for comparison without influence of heart rate correction.
- Parameter α of the regression model $QT = \beta \times \overline{RR}^{\alpha}$ (i.e., the slope of a parabolic log/log model) was obtained.
- Optimum regression residual (ORR) of the optimum QT/$\overline{RR}$ regression model was calculated.
- Mean 24-hour QTc value was derived.

Results were pooled together in amiodarone- and placebo-treated patients, distinguishing patients who did and did not suffer from arrhythmic death, which was used as the outcome event variable for the purpose of this study. Classification of the mode of death originally performed by the event committee of the trial was used.

The combination of amiodarone and beta-blocker is particularly beneficial.[2,3,17] Additional analysis was performed based on this combination, and the presence or absence of beta-blocker therapy in the amiodarone and placebo arm was considered.

Student's *t*-test for unpaired samples was used for group comparison. Kaplan-Meier probability curves of endpoint-free survival were obtained for patient groups stratified by the median value of each variable. The cumulative event-free survival probabilities were compared by log rank test.

Independent correlation of multiple variables with follow-up events was determined by Cox regression analysis, entering the QT/RR descriptors of parabolic slope, ORR, and mean QTc interval, together with previously established risk variables of left ventricular ejection fraction, age, sex, beta-blocker therapy, and heart rate variability index. Standard setting of the backward-stepwise method implemented using

TABLE 1
Baseline Patient Characteristics

	Amiodarone (n = 462)	Placebo (n = 404)	P†
Age (years)*	60.2 ± 10.0	60.8 ± 9.4	0.323
Men/women	391/71	345/59	0.754
Medical history			
Myocardial infarction	144	121	0.899
Angina pectoris	177	144	0.275
Hypertension	164	112	0.011
Diabetes	72	68	0.619
NYHA			
I	223	213	0.381
II	207	157	
III	31	31	
Baseline measures			
LVEF(%)	30.6 ± 6.8	30.3 ± 7.7	0.468
PBP (mm Hg)	118.7 ± 16.6	117.9 ± 17.3	0.459
DBP (mm Hg)	73.4 ± 10.5	74.2 ± 11.0	0.352
Heart rate (ms)	73.38 ± 14.49	73.25 ± 13.30	0.884
QRS duration (ms)	91.2 ± 18.6	91.2 ± 18.6	1.000
QT interval (ms)	389.34 ± 48.37	390.62 ± 47.37	0.694
Concomitant medication			
Thrombolytic	266	235	0.860
Digoxin	61	47	0.486
Beta-blocker	198	200	0.500
Calcium antagonist	70	62	0.937
ACE-inhibitor	260	219	0.542
Death during follow-up	(n = 59)	(n = 53)	0.879
Noncardiac	11	8	0.688
Cardiac	48	45	0.723
Nonarrhythmic	30	19	0.256
Arrhythmic	18	26	0.090

*Mean ± standard deviation, †P-value refers to comparison between amiodarone and placebo arm.

TABLE 2

QTc Intervals, QT/RR Slopes, and Optimum QT/RR Regression Residuum in Patients With and Without Arrhythmic Death on Amiodarone and Placebo

		Placebo	Amiodarone	P Value*
	Total population	425 ± 38	444 ± 37	1.3×10^{-12}
24-hour QTc interval	Arrhythmic death free	424 ± 37	444 ± 37	1.6×10^{-13}
	Arrhythmic death	443 ± 52	426 ± 34	0.122
	P value†	6.5×10^{-3}	2.6×10^{-2}	
Parabolic slope	Total population	0.48 ± 0.19	0.54 ± 0.24	6.3×10^{-6}
	Arrhythmic death free	0.48 ± 0.19	0.55 ± 0.24	4.4×10^{-5}
	Arrhythmic death	0.50 ± 0.19	0.44 ± 0.19	0.165
	P value†	0.317	4.0×10^{-2}	
Optimum regression residuum	Total population	13.9 ± 6.7	19.9 ± 9.4	8.2×10^{-26}
	Arrhythmic death free	13.9 ± 6.7	20.1 ± 9.4	4.1×10^{-24}
	Arrhythmic death	14.4 ± 6.2	14.3 ± 7.1	0.492
	P value†	0.381	4.4×10^{-3}	

The values shown are mean ± standard deviation, *P-value refers to comparison between amiodarone and placebo, †P-value refers to comparison between patients with and without arrhythmic death.

the Statistica package (version 6.1, StatSoft Inc., Tulsa, OK, USA) was used to compute the proportional hazard (Cox) regression model. Because the risk of arrhythmic mortality could not have been expected to increase linearly with the numerical values of the indices considered, the Cox regression analysis used QT/RR descriptors dichotomized at their median value, left ventricular ejection fraction dichotomized at 30%, and heart rate variability index dichotomized at 20 units.[4]

Data are presented as mean ± SD. $P < 0.05$ was considered statistically significant.

Results

Table 2 summarizes mean 24-hour values of QTc interval, parabolic slope, and ORR in patients with and without arrhythmic death on amiodarone and placebo. Table 3 lists the mean 24-hour values for patients with and without beta-blocker therapy on amiodarone and placebo. Figures 1 and 2 show QT/RR relationships in the investigated groups by plotting mean uncorrected QT intervals against 10-ms $\overline{RR}$ interval bins.

QTc Interval

Arrhythmic death was associated with significantly longer QTc intervals while on placebo. The opposite was true on amiodarone. Patients without endpoint events had highly significantly prolonged QTc intervals on amiodarone compared to placebo. This finding was not true for patients with events.

QT/RR Relationship

Patients without arrhythmic death in the amiodarone group had longer QT intervals at all $\overline{RR}$ intervals than the placebo group, with the difference more marked at longer $\overline{RR}$ intervals. However, victims of arrhythmic death on amiodarone had shorter QT intervals at all $\overline{RR}$ than patients without events on amiodarone. The QT/ $\overline{RR}$ relationship in patients with events was fairly similar on amiodarone and placebo.

Parabolic Slopes

Parabolic slopes in patients without events were significantly steeper on amiodarone than on placebo, whereas slopes in victims of arrhythmic death were not significantly different on amiodarone and on placebo. Amiodarone patients without outcome events had steeper slopes than those suffering from arrhythmic death.

Optimum Regression Residual

In patients without outcome events, ORR was highly significantly increased on amiodarone compared to placebo. This was not true in victims of arrhythmic death. Moreover, ORR in patients with and without events did not differ on

TABLE 3

QTc Intervals, QT/RR Slopes, and Optimum QT/RR Regression Residuum in Patients With and Without Beta-Blocker on Amiodarone and Placebo

		All	Placebo	Amiodarone	P Value*
24-hour QTc interval	On beta-blocker	434 ± 35	425 ± 36	444 ± 31	1.1×10^{-8}
	Off beta-blocker	435 ± 41	425 ± 40	443 ± 40	1.6×10^{-6}
	P value†	0.87	0.50	0.33	
Parabolic slope	On beta-blocker	0.53 ± 0.20	0.50 ± 0.17	0.56 ± 0.21	9.1×10^{-4}
	Off beta-blocker	0.50 ± 0.24	0.46 ± 0.20	0.54 ± 0.26	3.9×10^{-4}
	P value†	0.11	2.7×10^{-2}	0.17	
Optimum regression residuum	On beta-blocker	18.3 ± 9.3	15.0 ± 7.2	21.6 ± 10.0	3.3×10^{-13}
	Off beta-blocker	16.1 ± 8.1	12.8 ± 5.9	18.65 ± 8.7	1.2×10^{-15}
	P value†	2.6×10^{-4}	3.9×10^{-4}	4.7×10^{-4}	

The values shown are mean ± standard deviation, *P-value refers to comparison between amiodarone and placebo, †P-value refers to comparison between patients with and without beta-blocker.

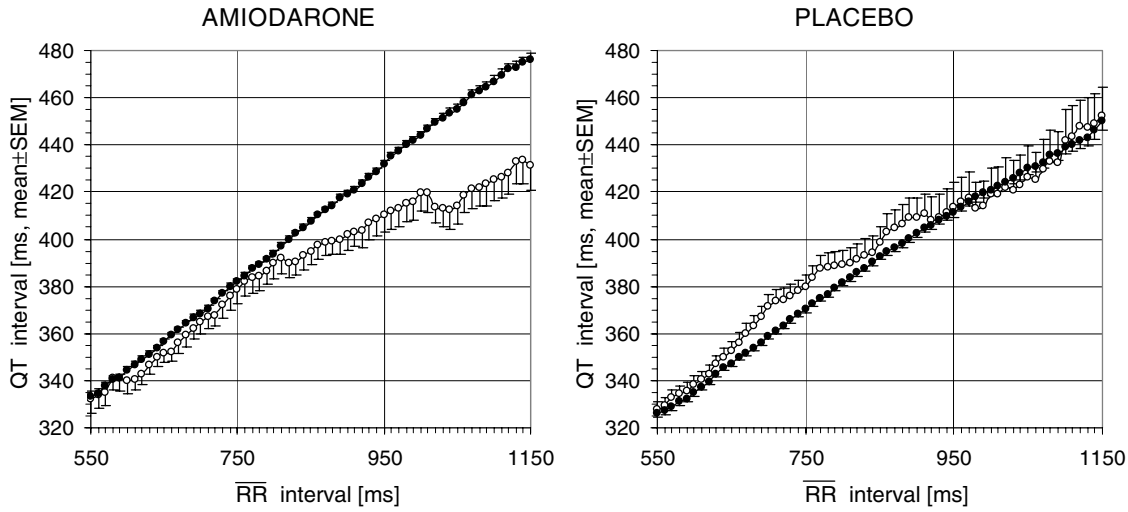

Figure 1. *The plots show uncorrected QT intervals for 10-ms $\overline{RR}$ interval bins in patients with (open circles) and without (closed circles) arrhythmic death on amiodarone (left panel) and placebo (right panel).*

placebo. However, ORR on amiodarone was very markedly and statistically highly significantly reduced in victims of arrhythmic death compared to others.

Beta-blocker therapy did not influence mean 24-hour QTc interval in either the amiodarone or the placebo arm. Parabolic slope values on beta-blocker were significantly steeper than those off beta-blocker on placebo but not on amiodarone. ORR was highly significantly increased by beta-blocker therapy in both the amiodarone and placebo arms.

Studying Kaplan-Meier event probabilities, reduced ORR proved to be a powerful risk stratifier of arrhythmic death among patients on amiodarone but not among those on placebo (Fig. 3). Figures 4 and 5 show Kaplan-Meier event probabilities for individually corrected QTc and parabolic slope.

As shown in Table 4, multivariate Cox regression analysis identified ORR <14.64 (median value), parabolic slope <0.506 (median value), and absence of beta-blocker treatment (marginally) as the only independent predictors of arrhythmic mortality in patients on amiodarone. No significant predictors of arrhythmic death were found in the placebo group.

Discussion

We found significant differences in QT/RR relationship and QTc interval duration not only between amiodarone- and placebo-treated postmyocardial infarction patients but also between victims of arrhythmic death and other patients on amiodarone. In particular, reduced ORR and flatter slope of the QT/RR relationship 1 month after onset of amiodarone treatment independently predicted arrhythmic death during follow-up.

Placebo Arm

As reported previously,[18] we found significantly longer QTc intervals in victims of arrhythmic death. In agreement

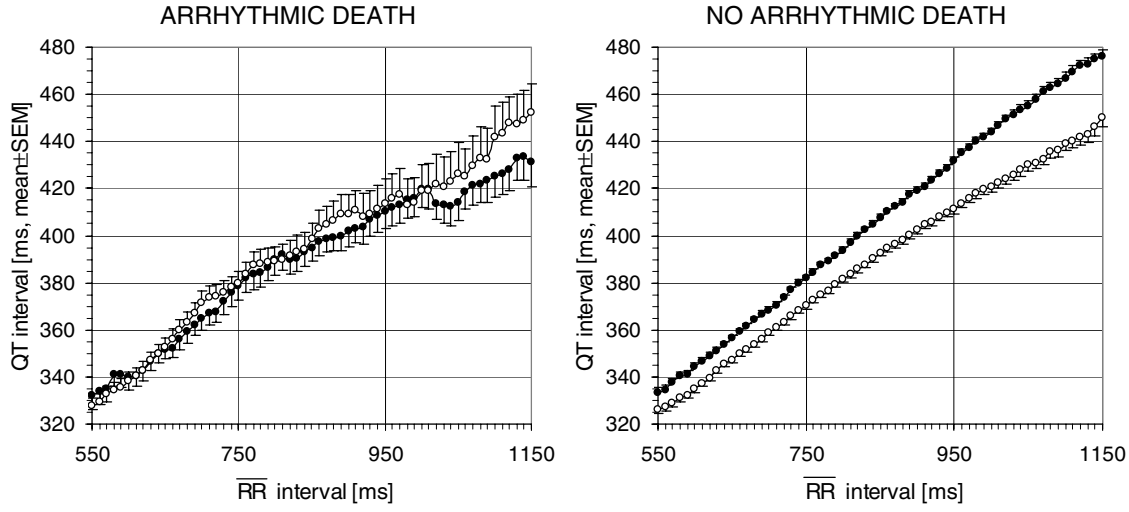

Figure 2. *The plots show uncorrected QT intervals for 10-ms $\overline{RR}$ interval bins in patients on placebo (open circles) and amiodarone (closed circles) with (left panel) and without (right panel) arrhythmic death.*

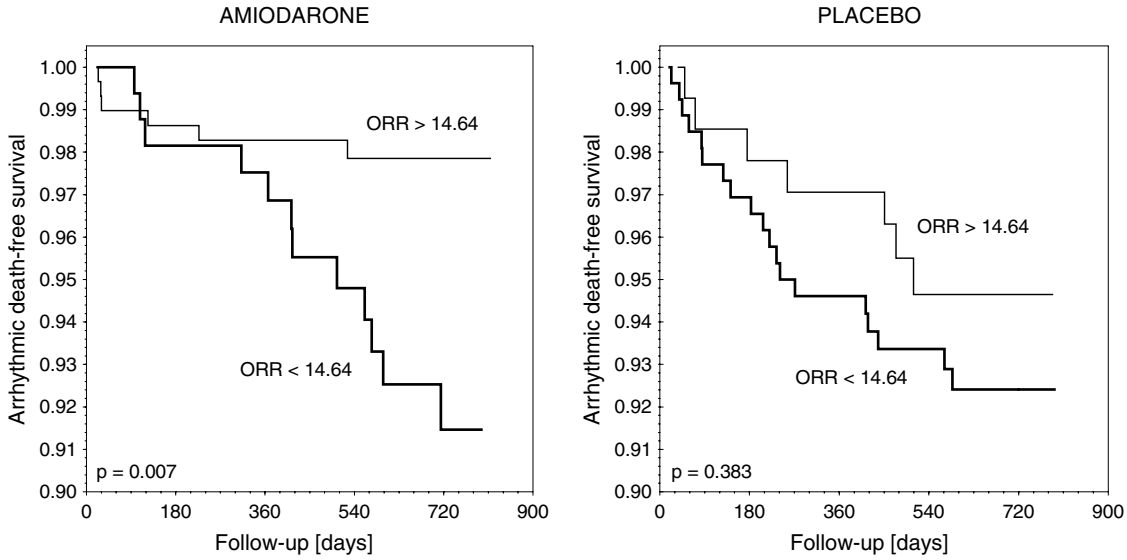

Figure 3. *Kaplan-Meier event probability curves (arrhythmic death free survival) for patient groups stratified by the optimum regression residuum above (fine line) and below (bold line) median value. Survival of patients on amiodarone and on placebo is shown in the left and right panel, respectively.*

with previous reports,[11] we found steeper QT/RR slopes in victims of arrhythmic death. Apart from confirmation of these previously know differences, the study findings within the placebo arm were of little interest. This contrasted with findings in the amiodarone arm.

Amiodarone Arm

Our finding of longer individually corrected 24-hour mean QTc intervals on amiodarone in patients without outcome events agrees with the known QTc prolonging effect of amiodarone.[19] However, the finding of shorter QTc intervals in patients with arrhythmic death than in others is counterintuitive. QTc prolongation on amiodarone has been observed repeatedly, but its value as a marker of drug efficacy remains controversial. Using inducibility of ventricular tachycardia in electrophysiologic studies[20,21] or recurrence of symptoms during follow-up[5,22] mostly in small heterogeneous populations, some authors reported the extent of QTc prolongation to be lower,[5] some higher,[22] and others not significantly different[20,21] in symptomatic patients. Our finding in a large homogeneous population of postmyocardial infarction patients that individually corrected QTc interval on amiodarone is significantly shorter in victims of arrhythmic death strongly suggests that the lack of QTc prolongation on amiodarone is a potent characteristic of inefficient treatment.

Imprecise heart rate correction can lead to artificial observations of drug-induced QT interval changes.[23] Because amiodarone slows heart rate, inaccurate formulas for calculation of QTc interval used in previous studies may have caused misleading results. This is not the problem with the individualized approach we used.

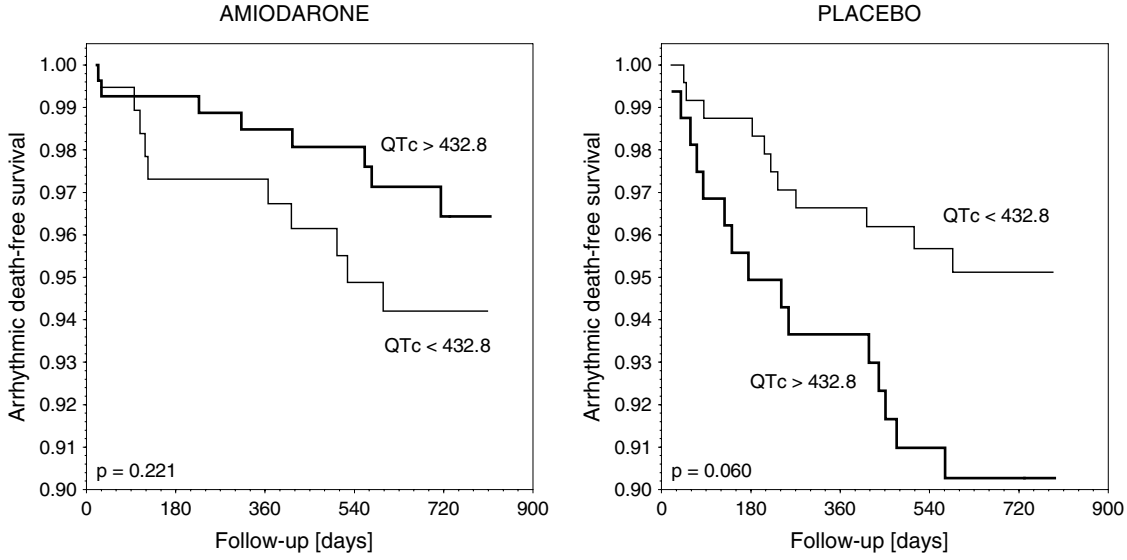

Figure 4. *Kaplan-Meier event probability curves (arrhythmic death free survival) for patient groups stratified by the individually corrected QTc above (bold line) and below (fine line) median value. Survival of patients on amiodarone and on placebo is shown in the left and right panel, respectively.*

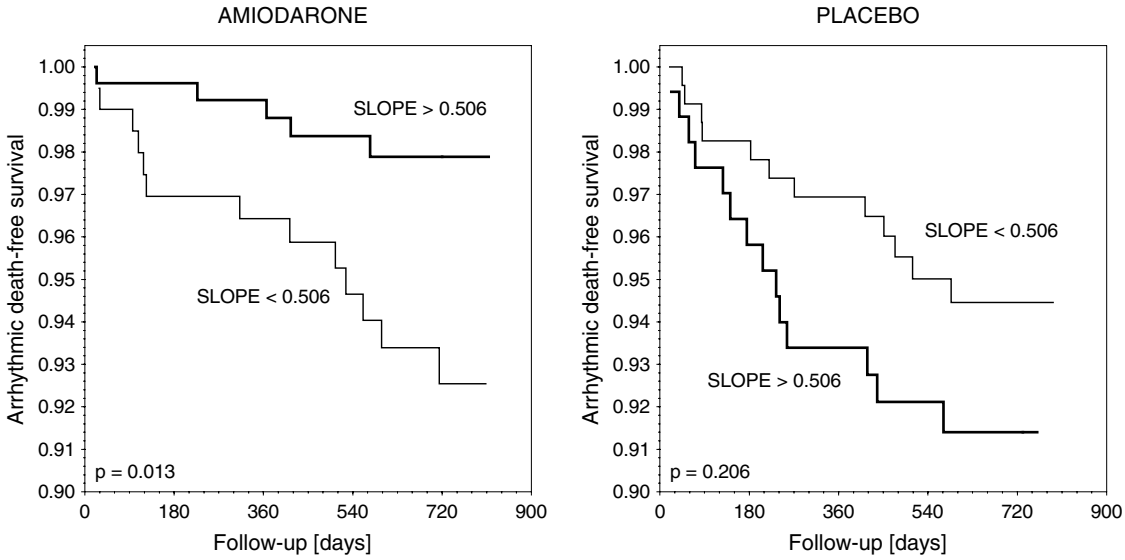

Figure 5. *Kaplan-Meier event probability curves (arrhythmic death free survival) for patient groups stratified by the parabolic slope above (bold line) and below (fine line) median value. Survival of patients on amiodarone and on placebo is shown in the left and right panel, respectively.*

Correlation between the extent of QTc prolongation and serum levels of amiodarone and desethylamiodarone remains controversial.[21,24] Similarly, correlation between serum levels and drug efficacy is problematic.[5,21,25] Thus, the difference in QTc intervals found in this study is not likely due to differences in serum drug levels.

Studies investigating the rate dependence of repolarization properties on amiodarone are inconsistent.[14,15,23,26-32] Many of the studies described an almost rate-independent prolongation of 90% action potential duration (APD_{90})[15,26] or QT interval.[14,27] The QT/RR relationship on amiodarone thus paralleled[26,27] or almost paralleled[14,15] that of controls in some studies. However, other studies described no QT prolongation on amiodarone at all[28] and a rate-independent APD prolongation in epicardium and endocardium but rate-dependent shortening of APD in the M region.[28,29] Only a few studies[23,30-32] reported rate-dependent (i.e., more marked at long cycle length) prolongation of APD_{90}[30-32] or QTc[23] on amiodarone. QT intervals in patients without endpoint events significantly prolonged on amiodarone at all cycle lengths compared to placebo. The difference was more marked at slower heart rates. This finding implies slopes on amiodarone are steeper than on placebo in these patients. Furthermore, slopes in patients with arrhythmic death on amiodarone were flatter than in other patients.

TABLE 4

Independent Prognostic Value of Variables Remaining in the Model on the Last Step of the Logistic Regression Carried out in the Amiodarone Arm with Arrhythmic Death as the Dependent Variable

Factor	Multivariate Cox Analysis	
	Hazard Ratio (95% Confidence Interval)	P Value
Slope	2.932 (1.000–8.598)	0.050
Optimum regression residual	2.769 (1.024–7.486)	0.045
Beta-blocker	3.444 (0.960–12.358)	0.058

Patients on amiodarone without events showed significantly higher ORR values than patients on placebo and victims of arrhythmic death on amiodarone. This was the only marker of QT/RR relationship highly significantly altered by additional beta-blocker therapy in both the placebo and the amiodarone arms.

The evidence strongly suggests a marked impact of efficient amiodarone therapy on the QT/RR relationship. Although steeper slopes reportedly are associated with higher arrhythmic risk[11] and higher sympathetic tone,[33] this characteristic is different on amiodarone. Increased ORR on amiodarone as well as beta-blocker might reflect a physiologically optimized and autonomically driven adaptation of repolarization to heart rate changes. The summation of beta-blocker and anti-adrenergic effects of amiodarone described to act via different mechanisms[34] also might explain highest slope and ORR values with this combination and the superior beneficial effect of this therapy.[2,3,17]

A more complex QT/RR relationship on amiodarone suggests that the drug unmasks other heart rate-independent modulations of QT interval duration. The ionic mechanism underlying APD prolongation on chronic amiodarone treatment is not fully understood. Recent studies suggest that both components of the delayed rectifier current I_{Kr} and I_{Ks}, as well as I_{K1}, are affected.[35,36]

Combined block of I_{Kr} and I_{Ks} prolongs APD in a reverse rate-dependent manner,[37] whereas APD prolongation after isolated blockade of I_{Ks} is rate independent. Similar to findings in theoretical ventricular cell models,[38] differences in the QT/RR relationship between long QT syndrome type 1 and type 2 patients confirm the importance of the I_{Kr}/I_{Ks} balance for the rate dependence of repolarization.[39] A drug that, among other effects, influences the I_{Kr}/I_{Ks} balance likely affects the adaptation of repolarization to heart rate.

Heart rate variability reflects the influence of sympathovagal modulations on the sinus node but does not provide information on the autonomic effects at the level of ventricular myocytes. This marker seems less appropriate for assessing the efficacy of a substance affecting mainly repolarization

electrophysiology within the ventricular myocardium. It is not surprising that heart rate variability assessed 1 month after randomization was not predictive for amiodarone efficacy in this study, whereas heart rate variability assessed before randomization identified patients at particularly high arrhythmic risk who therefore were benefiting from amiodarone treatment.[4] Nevertheless, combining the predictive power of these markers may help develop a strategy of using heart rate variability to identify patients at arrhythmic risk and then—after initiation of amiodarone treatment—investigating changes in QT/RR dynamics to select patients who, although at arrhythmic risk, likely will not benefit from therapy.

Study Limitations

The analysis was performed on the intention-to-treat basis at randomization. Some of the patients in the amiodarone arm likely discontinued study medication during follow-up. Because we found little differences in the placebo arm, exclusion of patients who discontinued medication would only make our findings more striking.

Ideally, the observations reported here would be supported by comparison of indices derived from prerandomization and postrandomization Holter recordings. Prerandomization Holter recordings were collected in EMIAT, but the recordings were not available for this study. Nevertheless, because treatment assignment to the amiodarone and placebo arms was randomized, no substantial prerandomization differences is expected to exist between the two arms. Statistically very highly significant differences between postrandomization indices found on placebo and amiodarone as shown in Table 2 ($P = 10^{-12}$ to 10^{-26}) likely did not exist in the prerandomization recordings.

The lack of prerandomization data limits the clinical extrapolation of our findings with respect to dichotomy values (the median value was used in this study). Because an individual-specific QT/RR relationship was repeatedly reported,[16] it does not seem appropriate to suggest absolute dichotomy values but rather a percentage of the baseline to characterize the beneficial changes and/or their absence. This was not possible in this study. Considering the placebo arm as "baseline," the absence of any change seems predictive of arrhythmic death on amiodarone, whereas increases by ~50% of ORR and ~10% of individually assessed QTc seem to predict treatment efficacy.

Any effect of amiodarone therapy can be assessed only after an initial loading phase. We used Holter recordings obtained 1 month after randomization, but several patients died before the follow-up investigation and are not considered in this study.

Information on serum drug levels was not available for this study. At the time of Holter recording, most of the subjects likely were affected by the drug due to administration of the loading dose and the drug's long half-life.

Measurement of QT interval is problematic, even more so in Holter recordings. However, such measurement is valid for both survivors and victims of arrhythmic death, so inaccuracies in determination of QT interval likely did not affect the differences between groups. Also, we did not blindly accept the automatic Holter analysis but carefully verified and corrected the measurement.

To allow meaningful statistics, we used only the QT/RR slope of the parabolic regression model. Although this model is not necessarily the optimum to fit the QT/RR curvature in some of the patients,[16] comparison of slopes of different regression models makes little sense. We repeated the calculations presented here with other QT/RR models and found practically identical results.

Conclusion

Chronic amiodarone treatment has marked effects on the QT/RR relationship. The effects are further increased by beta-blocker therapy. The lack of effects predicts arrhythmic death in postinfarction patients on amiodarone.

Although amiodarone currently is not used prophylactically in postinfarction patients, the drug—especially in combination with beta-blockers—remains a therapeutic option in many different patients, including those with no clear indication for an implantable defibrillator. Derived markers of amiodarone efficacy may help to optimize treatment by reducing side effects and identifying patients who are not protected by the treatment.

Appendix

The $\overline{RR}$ series were calculated for each patient as best expressing the QT dependence on previous cardiac cycles. For its determination, we searched for the optimum weight distribution corresponding to beats contained in a 5-minute window preceding each QT measurement (the criterion for "optimum" is explained next). For that purpose, a global optimization algorithm based on the Direct method[40] was implemented, in which the objective function to be minimized was defined at each weight vector $w = (w_1, \ldots, w_n)$ as the global residuum from fitting any of 10 previously selected regression models to the $[QT_i, \overline{RR}_i]$ data, with $\overline{RR}_i$ computed for each i^{th} beat as:

$$\overline{RR}_i = \sum_{j=i-n+1}^{i} w_j RR_j,$$

where n is the mean number of beats contained in the 5-minute window, calculated over the whole recording). Once the optimum weight combination $w = (w_1, \ldots, w_n)$ was identified for each patient, the corresponding $\overline{RR}$ series was computed as the moving window average of RR with weights of w.[41]

The ORR parameter is the residual of the QT/RR regression after the individual profile of QT/RR hysteresis[41] and the individual pattern of QT/RR profile[16] have been accounted for. In this way, ORR is a repolarization-related counterpart of heart rate variability measuring the variability of QT interval beyond the influence of heart rate and its variability.

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