Individual patterns of dynamic QT/RR relationship in survivors of acute myocardial infarction and their relationship to antiarrhythmic efficacy of amiodarone

by

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Abstract

Background: While amiodarone is an effective antiarrhythmic drug, it has serious side effects and conducted trials did not support its prophylactic uses in survivors of acute myocardial infarction. Still, it is possible that the prophylactic use of the drug has not been tested effectively. To optimise therapy outcome, markers of drug efficacy might be developed to identify patients who, though at arrhythmic risk, do not benefit from amiodarone treatment. We investigated descriptors of QT/RR relationship for their potential value in predicting inefficient treatment in amiodarone.

Methods and Results: The study used 866 Holter recordings (462 amiodarone, 404 placebo) obtained 1 month after randomisation in the EMIAT trial. 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 post myocardial infarction patients but also between patients with and without arrhythmic death on amiodarone (QTc with vs without arrhythmic death 426.30±33.93 ms vs 444.23±36.65 ms, $p=6.5\times10^{-3}$). In a multivariate analysis, reduced optimum regression residuum (14.33±7.08 vs 20.11±9.39, $p=4.4\times10^{-3}$) and flatter slope (0.44±0.19 vs 0.55±0.24, $p=4.0\times10^{-2}$) of the QT/RR relationship independently predicted arrhythmic death during follow-up.

Conclusions: 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.

Key words

Antiarrhythmia agents; repolarisation; 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 while failing to improve overall survival. This lack of overall prophylactic effect and the risk of serious adverse side-effects of chronic amiodarone treatment led, among others, to the conclusion that implantable defibrillators are presently the only prophylactic antiarrhythmic option in patients surviving acute myocardial infarction. There is, however, a possibility that the amiodarone trials have used a too broad enrolment criteria and that markers of arrhythmic risk could improve patient selection. Shortly after treatment initiation, tests of amiodarone efficacy may allow subjects to be identified, who, although at arrhythmic risk, would not benefit from the treatment. While a substudy of EMIAT (4) showed that depressed heart rate variability identifies post infarction patients who, due to their high arrhythmic risk, might benefit from prophylactic amiodarone treatment, studies of markers of therapeutic efficacy of amiodarone are inconsistent.

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

It has been previously reported that QT/RR relationship is altered after myocardial infarction (11) and that impaired adaptation of repolarisation to heart rate changes increases arrhythmic risk (12, 13). Also, the antiarrhythmic efficacy of amiodarone was partly explained by modulation of this repolarisation/rate adaptation, i.e. by an almost heart rate independent

prolongation of the QT interval (14, 15). We hypothesised 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 might be used as a marker of therapeutic efficacy.

Consequently, this study investigated 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 the EMIAT trial (2). In short, eligible patients were survivors of acute myocardial infarction aged 18 to 75 years who had a left ventricular ejection fraction ≤40% assessed by multiple-gated nuclear angiography between days 5 and 21 after the index infarction. A total of 866 24-hour 3-channel Holter recordings (462 on amiodarone, 404 on placebo) was obtained 1 month after treatment randomisation. All of these recordings were available for this study. Clinical characteristics of study population are shown in Table 1.

Data Preparation: A commercial Holter system (Pathfinder, Reynolds Medical Inc.) was used to measure RR and QT intervals in the 24-hours Holter recordings automatically on a beat-to-beat basis. The analysis was performed under careful visual control with manual artefact elimination. In each Holter lead, only beats with accepted QT and RR intervals were considered, and 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 the 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. These regression models (16) were designed to

cover a physiologic variety of QT/RR patterns, since it has been recently shown (16) that the patterns differ significantly between subjects. 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, this 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 was subsequently selected and used to calculate the individually optimised 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 ms to 1150 ms for comparison without influence of heart rate correction,
- parameter a of the regression model $QT = ß \times \overline{RR}^{a}$ (i.e. the slope of a parabolic log/log model) was obtained, and
- optimum regression residual (ORR) of the optimum QT/$\overline{RR}$ regression model was calculated, and
- mean 24-hour QTc value 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.

It has been shown recently that the combination of amiodarone and beta-blocker is particularly beneficial (2, 3, 17). Additional analysis was performed on basis of 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 the 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 other 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 in the Statistica package (vers 6.1, StatSoft Inc, Tulsa, OK, USA) was used for the computation of the proportional hazard (Cox) regression model. Since 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 dichotomised at their median value, left ventricular ejection fraction dichotomised at 30%, and heart rate variability index dichotomised at 20 units (4).

Data are presented as mean ± SD. A p value <0.05 was considered statistically significant.

Results

Table 2 summarises mean 24-hours values of QTc interval, parabolic slope and ORR in patients with and without arrhythmic death on amiodarone and placebo. Table 3 shows these mean 24-hours 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*: While on placebo, arrhythmic death was associated with significantly longer QTc intervals, the opposite was true on amiodarone. Patients without end-point events had highly significantly prolonged QTc intervals on amiodarone compared to placebo while this was not the case in 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 interval 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* 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.
- *ORR:* 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 placebo. However, ORR on amiodarone was very markedly and statistically highly significantly reduced in victims of arrhythmic death compared to others.
- Neither in the amiodarone nor the placebo arm was beta-blocker therapy of any influence on mean 24-hours QTc interval. On placebo but not on amiodarone parabolic slope values on beta-blocker were significantly steeper than those off beta-blocker. ORR was highly significantly increased by beta-blocker therapy in both the amiodarone and placebo arm.

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 (Figure 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 in QTc interval duration not only between amiodarone and placebo treated post myocardial 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 one 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. Also in agreement with previous reports (11) we found steeper QT/RR slopes in victims of arrhythmic death. Apart from the confirmation of these previously know differences, the study findings within the placebo arm were of little interest. This contrasted with the amiodarone arm.

Amiodarone arm: Our finding of longer individually corrected 24-hours mean QTc intervals on amiodarone in patients without outcome events agrees with the known QTc prolonging effect of the drug (19). However, the finding of shorter QTc intervals in patients with arrhythmic death than in others is counter intuitive. QTc prolongation on amiodarone has been appreciated 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 (22, 5) mostly in small heterogeneous populations, some authors reported the extent of QTc prolongation to be lower (5) some to be higher (22) and others not to be significantly different (20, 21) in symptomatic patients. Our finding in a large homogeneous population of post-myocardial infarction patients of individually corrected QTc interval on amiodarone being significantly shorter in victims of arrhythmic death strongly suggests that the lack of QTc prolongation on amiodarone is a potent characteristic of inefficient treatment.

Imprecision in heart rate correction may lead to artificial observations of drug induced QT interval changes (23). Since amiodarone slows heart rate inaccurate formulae for calculation

of QTc interval used in previous studies may have caused misleading results. This is not the problem with the individualised approach we have used.

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, it is most unlikely that the difference in QTc intervals found in this study is due to differences in serum drug levels.

Studies investigating the rate dependence of repolarisation properties on amiodarone (14, 15, 23, 26-32) are inconsistent. Many of them 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, others 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 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. Compared to placebo we found QT intervals in patients without endpoint events significantly prolonged on amiodarone at all cycle lengths with the difference being more marked at slower heart rates. This implies slopes on amiodarone being steeper than on placebo in these patients. Furthermore, slopes in patients with arrhythmic death on amiodarone were flatter than in others.

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

This evidence strongly suggests a marked impact of efficient amiodarone therapy on QT/RR relationship. Although steeper slopes were reported to be 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 optimised and autonomically driven adaptation of repolarisation to heart rate changes. The summation of beta-blocker and anti-adrenergic effects of amiodarone described to act via different mechanisms (34) might also explain highest slope and ORR values with this combination and perhaps also the superior beneficial effect of this therapy (2, 3, 17).

A more complex QT/RR relationship on amiodarone might also suggest 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 (35, 36) suggested that both components of the delayed rectifier current I_{Kr} and I_{Ks} as well as I_{K1} are affected.

It has been shown (37) that combined block of both I_{Kr} and I_{Ks} prolongs APD in a reverse rate dependent manner, whereas APD prolongation after isolated blockade of I_{Ks} is rate independent. Similar to findings in theoretical ventricular cell models (38), differences in QT/RR relationship between long QT syndrome type1 and type2 patients (39) confirm this importance of the I_{Kr}/I_{Ks} balance for the rate dependence of repolarisation. Thus, a drug which, beside other effects, also affects the I_{Kr}/I_{Ks} balance, is likely to affect the adaptation of repolarisation to heart rate.

While heart rate variability reflects the influence of sympathovagal modulations on the sinus node, it does not provide information on the autonomic effects at the level of ventricular myocytes. Thus, for an assessment of the efficacy of a substance affecting mainly repolarisation electrophysiology within the ventricular myocardium, this marker seems to be less appropriate. It is therefore not surprising that heart rate variability, assessed at 1 month visit after randomisation, was not predictive for amiodarone efficacy in this study, whereas heart rate variability assessed bore randomisation was shown to identify patients at particularly high arrhythmic risk who therefore were profiting from amiodarone treatment (4). Nevertheless, combining the predictive power of these markers might help to develop a strategy of firstly using heart rate variability to identify those patients at particular arrhythmic risk and

subsequently, after the initiation of amiodarone treatment, investigating changes in QT/RR dynamics to select those who, though at arrhythmic risk, are unlikely to profit from the therapy.

Limitations of the study: The analysis was performed on the intention to treat basis at randomisation. It is likely that some of the patients in the amiodarone arm discontinued study medication during follow-up. However, since we found little differences in the placebo arm, exclusion of patients with discontinued medication could only make our findings even more striking.

Ideally, the observations reported here should have been supported by the comparison of indices derived from pre- and post-randomisation Holter recordings. While pre-randomisation Holter recordings were collected in EMIAT, these recordings have not been available for this study. None the less, as the treatment assignment to amiodarone and placebo arms was randomised, it is reasonable to expect that no substantial pre-randomisation differences existed between the two arms. Statistically very highly significant differences between post-randomisation indices found on placebo and amiodarone as shown in Table 2 ($p = 10^{-12}$ to 10^{-26}) have extremely unlikely existed in the pre-randomisation recordings.

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

Any effect of amiodarone therapy can only be assessed after an initial loading phase. Since we used Holter recordings obtained 1-month after randomisation, several patients have died before this follow-up investigation and could not be considered in this study.

Although information on serum drug levels was not available for this study it is likely that due to administration of a loading dose and long half-life of the drug, most of the subjects were affected by the drug at the time of the Holter recording.

Measurement of the QT interval is known to be problematic and even more so in Holter recordings. However, since this is valid for both survivors and victims of arrhythmic death, it is unlikely that inaccuracies in determination of QT interval would have affected the differences between groups. Also, we have not accepted the automatic Holter analysis blindly but carefully verified and corrected the measurement.

To allow meaningful statistics, we have used only the QT/RR slope of the parabolic regression model. While this model was 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 have repeated the calculations presented here with other QT/RR models and found practically identical results.

Summary

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

Although amiodarone is not currently used prophylactically in post infarction patients, the drug especially in combination with beta-blockers remains a therapeutic option in many areas including those of no clear indication for implantable defibrillator. Derived markers of amiodarone efficacy may thus help to optimise treatment by reducing side effects and by 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 optimisation algorithm based on the Direct method (40) was implemented, in which the objective function to be minimised was defined at each weight vector $w = (w_1, \mathrm{K}\ , w_n)$ as the global residuum from fitting any of ten previously selected regression models to the $[QT_i\ , \overline{RR}_i]$ data, with $\overline{RR}_i$ computed for each *i*-th beat as

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

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

Thus, 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 repolarisation-related counter-part of heart rate variability measuring the variability of QT interval beyond the influence of heart rate and its variability.

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Figure Legends

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).

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.

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.

Tables

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
SBP (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			
Thrombolytics	266	235	0.860
Digoxin	61	47	0.486
Beta_blocker	198	200	0.050
Calcium_antagonist	70	62	0.937
ACE_inhibitors	260	219	0.542
Death during follow-up	(n=59)	(n=53)	0.879
Non-cardiac	11	8	0.688
Cardiac	48	45	0.723
Non-arrhythmic	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*
24-hours QTc interval	Total population	425±38	444±37	1.3×10^{-12}
	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.

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-hours 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.

Table 4

Independent prognostic value of the variables remaining in the model on the last step of the logistic regression carried out in the amiodarone arm with arrhythmic death as dependent variable.

Factor	Multivariate Cox Analysis	
	Hazard ratio (95% confidence interval)	p-value
Slope	2.932 (1.000 – 8.598)	0.050
ORR	2.769 (1.024 – 7.486)	0.045
β - blockers	3.444 (0.960 – 12.358)	0.058

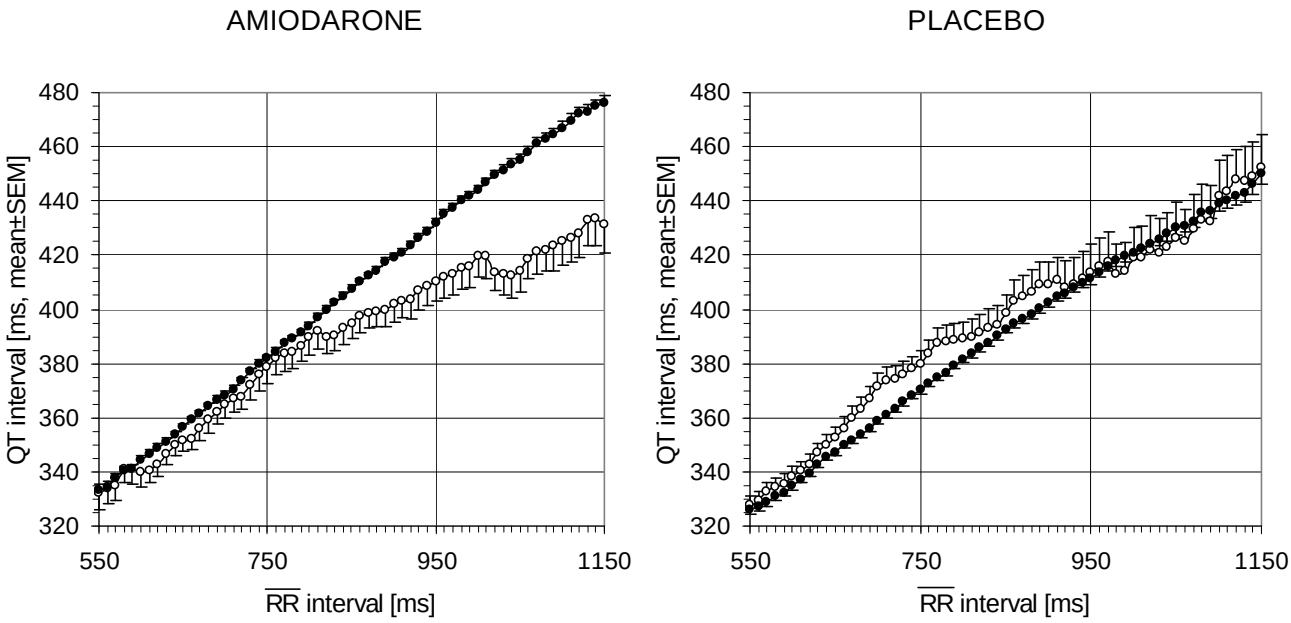

AMIODARONE
PLACEBO
480
460
440
420
400
380
360
340
320
QT interval [ms, mean±SEM]
550
750
950
1150
RR interval [ms]

Figure 1

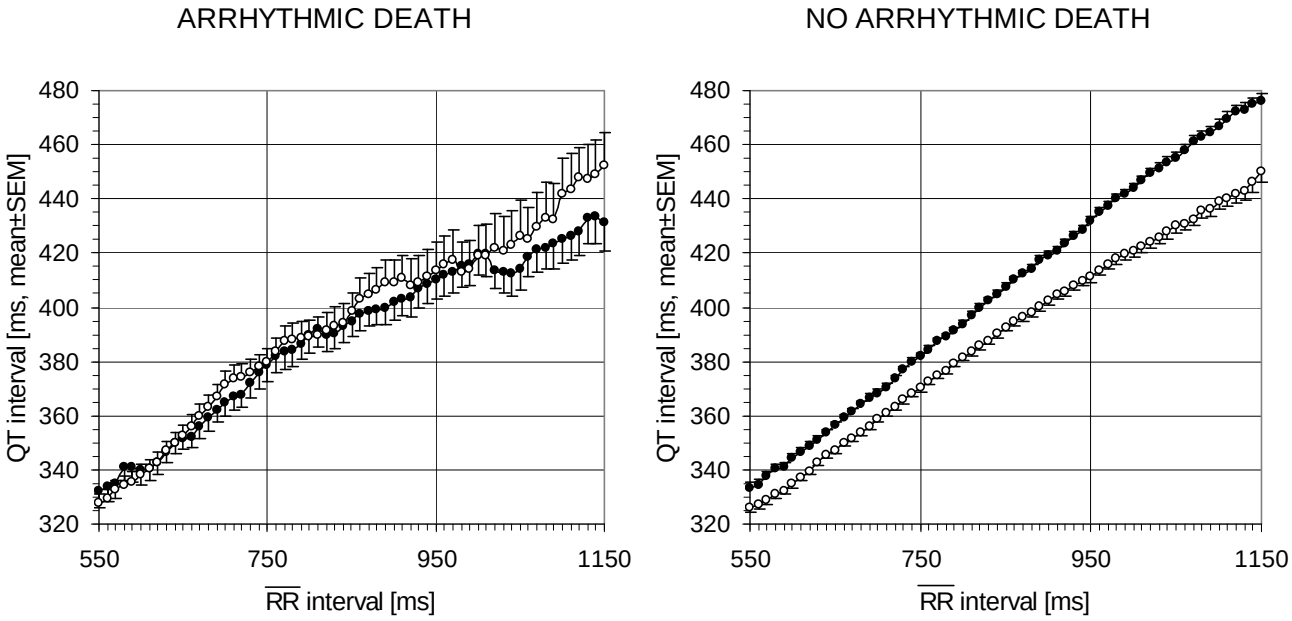

ARRHYTHMIC DEATH
NO ARRHYTHMIC DEATH
QT interval [ms, mean±SEM]
480
460
440
420
400
380
360
340
320
550
750
950
1150
RR interval [ms]

Figure 2

Figure 3

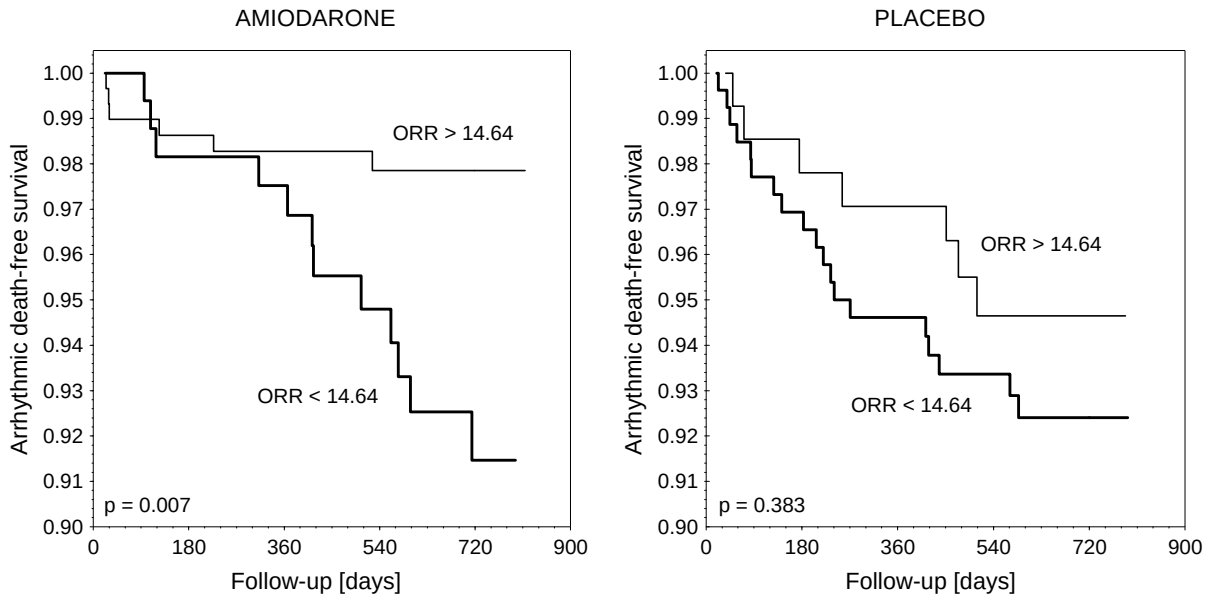

AMIODARONE
PLACEBO
Arrhythmic death-free survival
1.00
0.99
0.98
0.97
0.96
0.95
0.94
0.93
0.92
0.91
0.90
ORR > 14.64
ORR < 14.64
p = 0.007
p = 0.383
0
180
360
540
720
900
Follow-up [days]

Figure 4

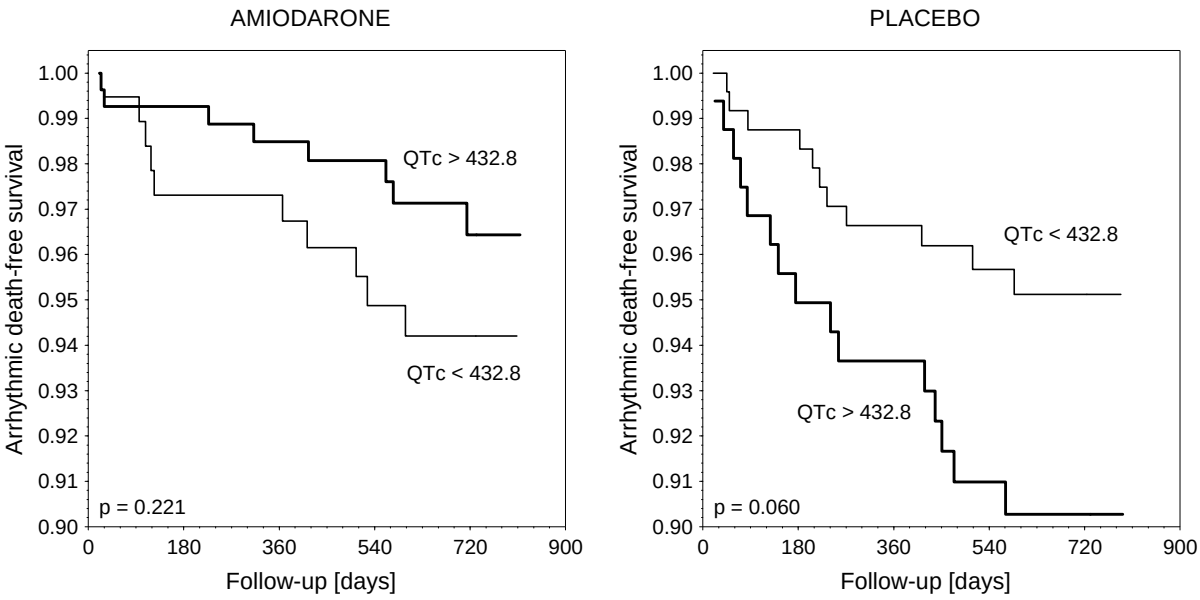
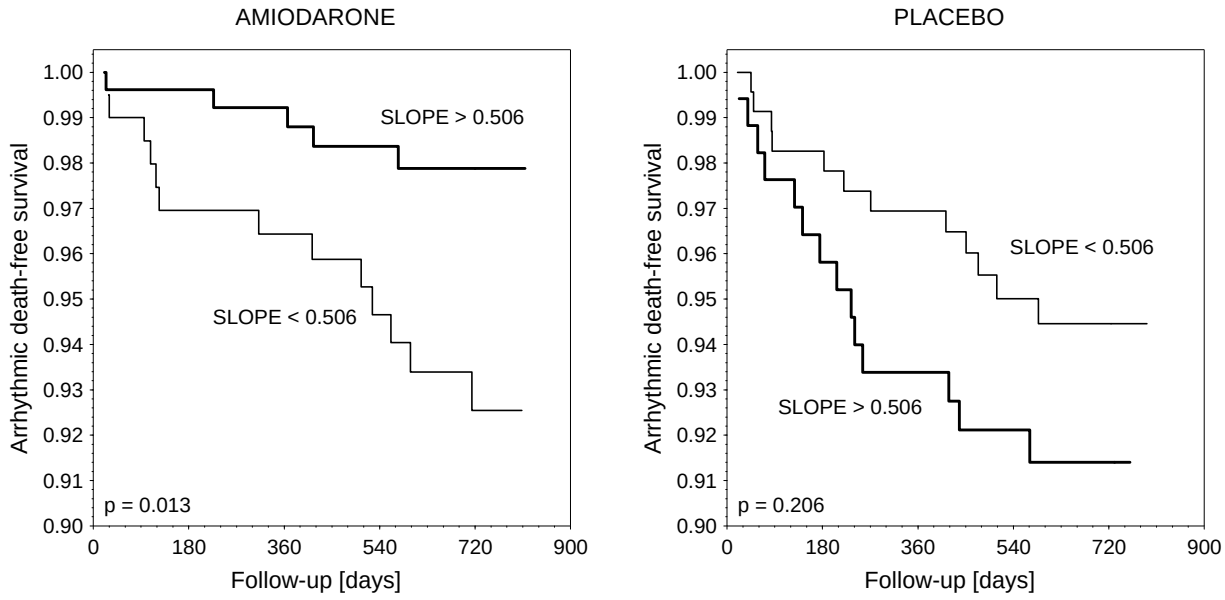

AMIODARONE
PLACEBO
Arrhythmic death-free survival
1.00
0.99
0.98
0.97
0.96
0.95
0.94
0.93
0.92
0.91
0.90
QTc > 432.8
QTc < 432.8
p = 0.221
p = 0.060
0
180
360
540
720
900
Follow-up [days]

Figure 5


AMIODARONE
PLACEBO
Arrhythmic death-free survival
1.00
0.99
0.98
0.97
0.96
0.95
0.94
0.93
0.92
0.91
0.90
SLOPE > 0.506
SLOPE < 0.506
p = 0.013
SLOPE < 0.506
SLOPE > 0.506
p = 0.206
0
180
360
540
720
900
Follow-up [days]