

ORIGINAL ARTICLE

Risk Stratification in the Long-QT Syndrome

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ABSTRACT

BACKGROUND

Mutations in potassium-channel genes *KCNQ1* (LQT1 locus) and *KCNH2* (LQT2 locus) and the sodium-channel gene *SCN5A* (LQT3 locus) are the most common causes of the long-QT syndrome. We stratified risk according to the genotype, in conjunction with other clinical variables such as sex and the length of the QT interval.

METHODS

We evaluated 647 patients (386 with a mutation at the LQT1 locus, 206 with a mutation at the LQT2 locus, and 55 with a mutation at the LQT3 locus) from 193 consecutively genotyped families with the long-QT syndrome. The cumulative probability of a first cardiac event, defined as the occurrence of syncope, cardiac arrest, or sudden death before the age of 40 years and before the initiation of therapy, was determined according to genotype, sex, and the QT interval corrected for heart rate (QTc). Within each genotype we also assessed risk in the four categories derived from the combination of sex and QTc (<500 msec or \geq 500 msec).

RESULTS

The incidence of a first cardiac event before the age of 40 years and before the initiation of therapy was lower among patients with a mutation at the LQT1 locus (30 percent) than among those with a mutation at the LQT2 locus (46 percent) or those with a mutation at the LQT3 locus (42 percent) ($P < 0.001$ by Fisher's exact test). Multivariate analysis showed that the genetic locus and the QTc, but not sex, were independent predictors of risk. The QTc was an independent predictor of risk among patients with a mutation at the LQT1 locus and those with a mutation at the LQT2 locus but not among those with a mutation at the LQT3 locus, whereas sex was an independent predictor of events only among those with a mutation at the LQT3 locus.

CONCLUSIONS

The locus of the causative mutation affects the clinical course of the long-QT syndrome and modulates the effects of the QTc and sex on clinical manifestations. We propose an approach to risk stratification based on these variables.

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THE ROMANO-WARD VARIANT OF THE long-QT syndrome is a genetically transmitted disorder characterized by prolonged ventricular repolarization that predisposes carriers to life-threatening arrhythmias.¹ Almost 40 years after its initial description,^{2,3} the natural history of the syndrome remains incompletely characterized and approaches to risk stratification are not well defined. These gaps in knowledge are largely due to the fact that the long-QT syndrome is uncommon, cardiac events may be separated by long periods without symptoms, and the initial manifestation may occur late in life. Five genes have been linked to the long-QT syndrome,^{4,5} and studies of the genotype and phenotype have identified clinical profiles that distinguish each genetic subgroup.⁶⁻¹⁰ However, information on the occurrence of events in each genetic subgroup is limited and thus insufficient for risk stratification. Such information would be useful in making decisions about treatment, particularly for patients who are asymptomatic. The objectives of this study were to define the cumulative probability of a first cardiac event (defined as syncope, cardiac arrest, or sudden death) before therapy (i.e., the natural history of the disease) and to analyze the complex interplay among the genetic locus, sex, and the duration of repolarization, which determines the probability of cardiac events in the long-QT syndrome. In addition, we examined whether the available data might provide insights into risk stratification.

METHODS

STUDY POPULATION

We report data from 193 consecutively genotyped families with the long-QT syndrome owing to mutations at the LQT1 locus of the *KCNQ1* potassium-channel gene in 104 families, the LQT2 locus of the *KCNH2* potassium-channel gene in 68 families, and the LQT3 locus of the *SCN5A* sodium-channel gene in 21 families. We examined a total of 647 patients, of whom 580 were genotyped in our laboratories and 67 died suddenly and unexpectedly before the age of 40 years and were categorized as affected by the long-QT syndrome.

Data on natural history were collected from the overall population of 647 patients, and the cumulative probability of cardiac events was calculated from data from the 580 patients with an available electrocardiogram. Cardiac events were defined as syncope, cardiac arrest, and sudden death. All

probands and family members or their guardians provided written informed consent for clinical and genetic evaluation. Protocols were approved by the institutional review board of the Fondazione Salvatore Maugeri.

CLINICAL PHENOTYPE

We either evaluated patients at our center or examined medical records (including electrocardiograms) submitted by referring physicians. The QT interval corrected for heart rate (QTc) was measured in lead II (or lead I or III if it could not be measured in lead II)⁸ from 12-lead electrocardiograms with the use of Bazett's formula. Quartiles of QTc were determined in the overall population and in each genetic subgroup. Clinical data were prospectively collected at follow-up visits or by telephone contacts and included demographic data, personal and family history, symptoms, and therapy. Data were stored in a computerized data base custom-made at the Fondazione Salvatore Maugeri.

GENETIC ANALYSIS

Patients were consecutively genotyped at the molecular cardiology laboratories of the Maugeri Foundation between June 1996 and December 2001 and classified as carriers of a single mutation on *KCNQ1*, *KCNH2*, or *SCN5A*. DNA was extracted from peripheral-blood lymphocytes according to standard procedures. Primer pairs for *KCNQ1*, *KCNH2*, and *SCN5A* amplification were used.^{11,12} Single-strand conformational polymorphism analysis, denaturing high-performance liquid chromatography (Wave Transgenomics), or both were performed with amplified genomic DNA. For samples with abnormal patterns, both strands were sequenced with use of an automated DNA analyzer (ABI Prism 310, ABI). A panel of results from 400 healthy persons was used as the control; a mutation was defined as a DNA change that modified the encoded protein and that was not present in any control.

STATISTICAL ANALYSIS

The clinical features and end points of the analysis were assessed with the use of the SPSS software (version 10.0): analysis of variance, paired and unpaired t-tests, and cross-tabulations with Fisher's exact test were used as appropriate. The cumulative probability of a first cardiac arrest or sudden death before the age of 40 years and before therapy and the cumulative probability of a first cardiac event (syncope, cardiac arrest, or sudden death) before the

age of 40 years and before therapy were determined in the entire population and in each genetic subgroup with the use of the life-table method of Kaplan and Meier, and the results were compared with use of the log-rank test with Bonferroni's correction for multiplicity. Cox multivariate survivorship analyses were performed to evaluate the statistical significance and independence of predictors of a first cardiac arrest or sudden death and of a first cardiac event alone.

RESULTS

The population under study included 647 patients from 193 families with the long-QT syndrome: 386 with a mutation at the LQT1 locus, 206 with a mutation at the LQT2 locus, and 55 with a mutation at the LQT3 locus.

NATURAL HISTORY

Over a mean observation period of 28 years, 87 patients (13 percent) had cardiac arrest or died suddenly before the age of 40 years and before the initiation of any treatment related to the long-QT syndrome (Table 1). The mean (\pm SD) observation period was similar among the genetic subgroups (29 \pm 20 years in the group with a mutation at the LQT1 locus, 28 \pm 18 years in the group with a mutation at the LQT2 locus, and 25 \pm 18 years in the group with a mutation at the LQT3 locus). The cumulative incidence of cardiac arrest or sudden death

was similar between the sexes: 14 percent among women (53 of 372) and 12 percent among men (34 of 275, $P=0.56$). The incidence of cardiac arrest or sudden death was 20 percent among patients with a mutation at the LQT2 locus (41 of 206), 16.4 percent among patients with a mutation at the LQT3 locus (9 of 55), and 10 percent among patients with a mutation at the LQT1 locus (37 of 386). Kaplan-Meier analysis showed that the cumulative rate of survival without cardiac arrest or sudden death differed among the subgroups ($P=0.002$ by the log-rank test). Specifically, the cumulative survival rate was lower among patients with a mutation at the LQT2 locus than among those with a mutation at the LQT1 locus ($P<0.001$ by the log-rank test), and there was a trend toward a lower cumulative survival rate among those with a mutation at the LQT3 locus than among those with a mutation at the LQT1 locus ($P=0.07$ by the log-rank test).

The same pattern was observed when the analysis included all first cardiac events — syncope, cardiac arrest, and sudden death — since there was no significant sex-related difference, but there was a significant difference related to the genetic locus ($P=0.002$ by the log-rank test) in the overall population. Pairwise analysis showed a significantly higher number of events among patients with a mutation at the LQT2 locus than among those with a mutation at the LQT1 locus ($P<0.001$ by the log-rank test), and there was a trend toward more events among patients with a mutation at the LQT3 locus than among those with a mutation at the LQT1 locus ($P=0.05$ by the log-rank test) (Table 2).

The mean age at the time of the first cardiac event (before the age of 40 years) was not significantly different among the three subgroups: 13 \pm 9

Table 1. Incidence of a First Cardiac Arrest or Sudden Death before the Age of 40 Years and before Therapy among Patients with the Long-QT Syndrome, According to the Genetic Locus of the Mutation.

| Locus and Sex | All Patients | Patients with Sudden Death or Cardiac Arrest | Incidence |
|---------------|--------------|--|-----------|
| | | number | %/yr |
| LQT1 | | | |
| Female sex | 217 | 20 | 0.28 |
| Male sex | 169 | 17 | 0.33 |
| Total | 386 | 37 | 0.30 |
| LQT2 | | | |
| Female sex | 125 | 30 | 0.82 |
| Male sex | 81 | 11 | 0.46 |
| Total | 206 | 41 | 0.60 |
| LQT3 | | | |
| Female sex | 30 | 3 | 0.30 |
| Male sex | 25 | 6 | 0.96 |
| Total | 55 | 9 | 0.56 |

Table 2. Incidence of a First Cardiac Event before the Age of 40 Years and before Therapy in Patients with the Long-QT Syndrome, According to the Genetic Locus of the Mutation.*

| Locus | Total No. of Patients | No. with an Event (%) |
|-------|-----------------------|-----------------------|
| LQT1 | 386 | 116 (30) |
| LQT2 | 206 | 95 (46) |
| LQT3 | 55 | 23 (42) |
| Total | 647 | 234 (36) |

* Cardiac events include syncope, cardiac arrest, and sudden death.

years in the LQT1 subgroup, 18 ± 10 years in the LQT2 subgroup, and 16 ± 10 years in the LQT3 subgroup. The age at the time of the first cardiac event was younger in male patients than in female patients (13 ± 9 vs. 20 ± 14 years, $P < 0.001$). Specifically, it was 11 ± 9 years among male patients with a mutation at the LQT1 locus and 18 ± 15 years among female patients ($P = 0.006$), 13 ± 10 years among male patients with a mutation at the LQT2 locus and 22 ± 12 years among female patients ($P = 0.003$), and 16 ± 12 years among male patients with a mutation at the LQT3 locus and 23 ± 18 years among female patients ($P = 0.24$).

RISK STRATIFICATION

We considered the association of genetic locus, sex, and QTc with the risk of a first cardiac event before the age of 40 years and before therapy in the 580 patients entered in the risk-stratification analysis: 355 patients with a mutation at the LQT1 locus, 176 with a mutation at the LQT2 locus, and 49 with a mutation at the LQT3 locus. Kaplan–Meier analysis showed a differential cumulative event-free survival among the three genetic subgroups ($P = 0.007$ by the log-rank test) (Fig. 1). Kaplan–Meier analysis showed that in the entire population, sex-related differences were not statistically significant ($P = 0.06$ by the log-rank test). When the analysis was repeated for each subgroup, sex had no influence among patients with a mutation at the LQT1 locus ($P = 0.18$), whereas female patients with a mutation at the LQT2 locus had a higher risk than male patients ($P = 0.02$ by the log-rank test), and there was a trend toward a higher risk among male patients with a mutation at the LQT3 locus than among female patients ($P = 0.048$ by the log-rank test). This finding supports the observation that the annual incidence of a first cardiac arrest or sudden death was highest among female patients with a mutation at the LQT2 locus (0.82 per year) and male patients with a mutation at the LQT3 locus (0.96 per year) (Table 1). Thus, the role of sex varies according to the genetic locus.

When QTc was examined, significant differences were observed among the three subgroups. The mean QTc was 466 ± 44 msec among patients with a mutation at the LQT1 locus, 490 ± 49 msec among those with a mutation at the LQT2 locus, and 496 ± 49 msec among those with a mutation at the LQT3 locus ($P < 0.001$ for the comparisons of the LQT1 group with the LQT2 group and the LQT1 group with the LQT3 group, and $P = 0.22$ for the compar-

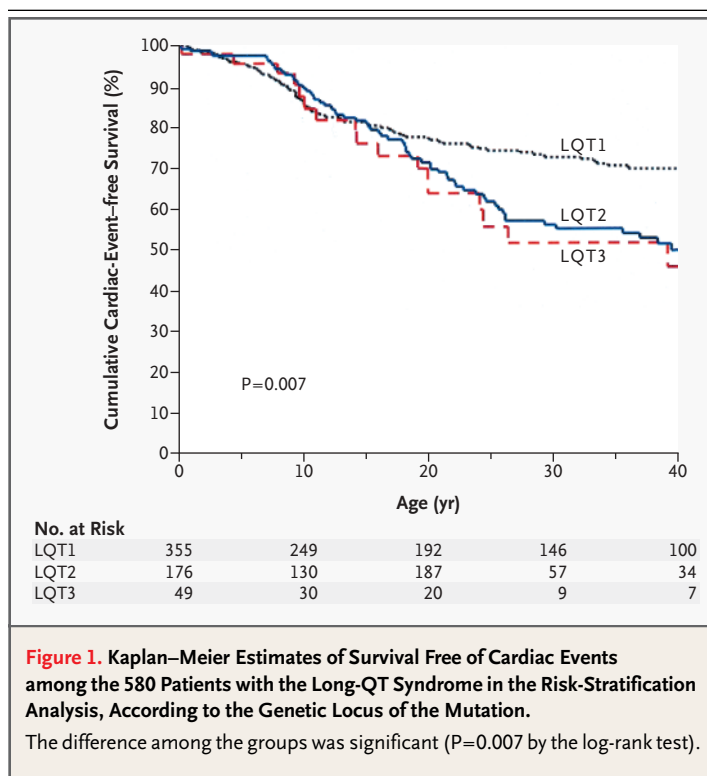
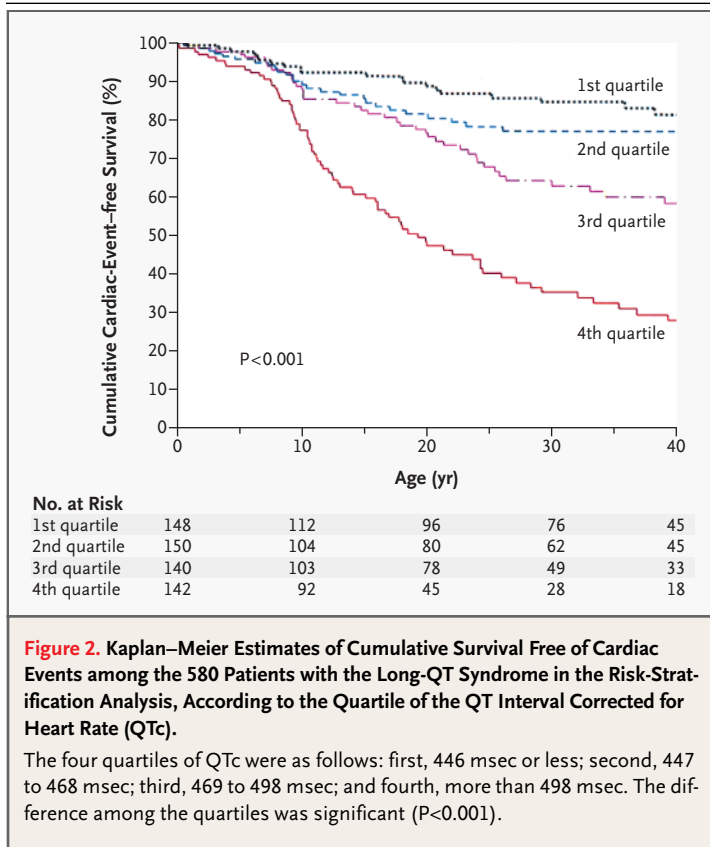


Figure 1. Kaplan–Meier Estimates of Survival Free of Cardiac Events among the 580 Patients with the Long-QT Syndrome in the Risk-Stratification Analysis, According to the Genetic Locus of the Mutation.

The difference among the groups was significant ($P = 0.007$ by the log-rank test).

son of the LQT2 group with the LQT3 group). In each subgroup the QTc of patients who had cardiac events was significantly longer than that of asymptomatic patients (488 ± 47 msec vs. 459 ± 40 msec in the LQT1 group, $P < 0.001$; 519 ± 55 msec vs. 472 ± 35 msec in the LQT2 group, $P < 0.001$; and 523 ± 55 msec vs. 481 ± 38 msec in the LQT3 subgroup, $P = 0.003$). The percentage of genetically affected patients with a normal QTc (silent mutation carriers) was significantly higher ($P < 0.001$) in the LQT1 group (36 percent) than in the LQT2 group (19 percent) or the LQT3 group (10 percent).

When the cumulative event-free survival was analyzed in the 580 patients in the risk-stratification analysis according to the quartile of QTc, there was a progressive decrease in survival at longer QTc values (Fig. 2). Since the QTc differed among the three subgroups, we performed the analysis using both quartiles of QTc derived from the entire population under study and the quartiles in each subgroup (locus-specific quartiles). Both analyses demonstrated an increased probability of a first cardiac event before the age of 40 years and before therapy among patients with a QTc in the upper quartiles ($P < 0.001$ by the log-rank test). Kaplan–Meier analysis showed that the cumulative probability of a first cardiac



event was higher among patients with a longer QTc in the LQT1 group and the LQT2 group ($P < 0.001$ for both comparisons), but not among those in the LQT3 group ($P = 0.23$).

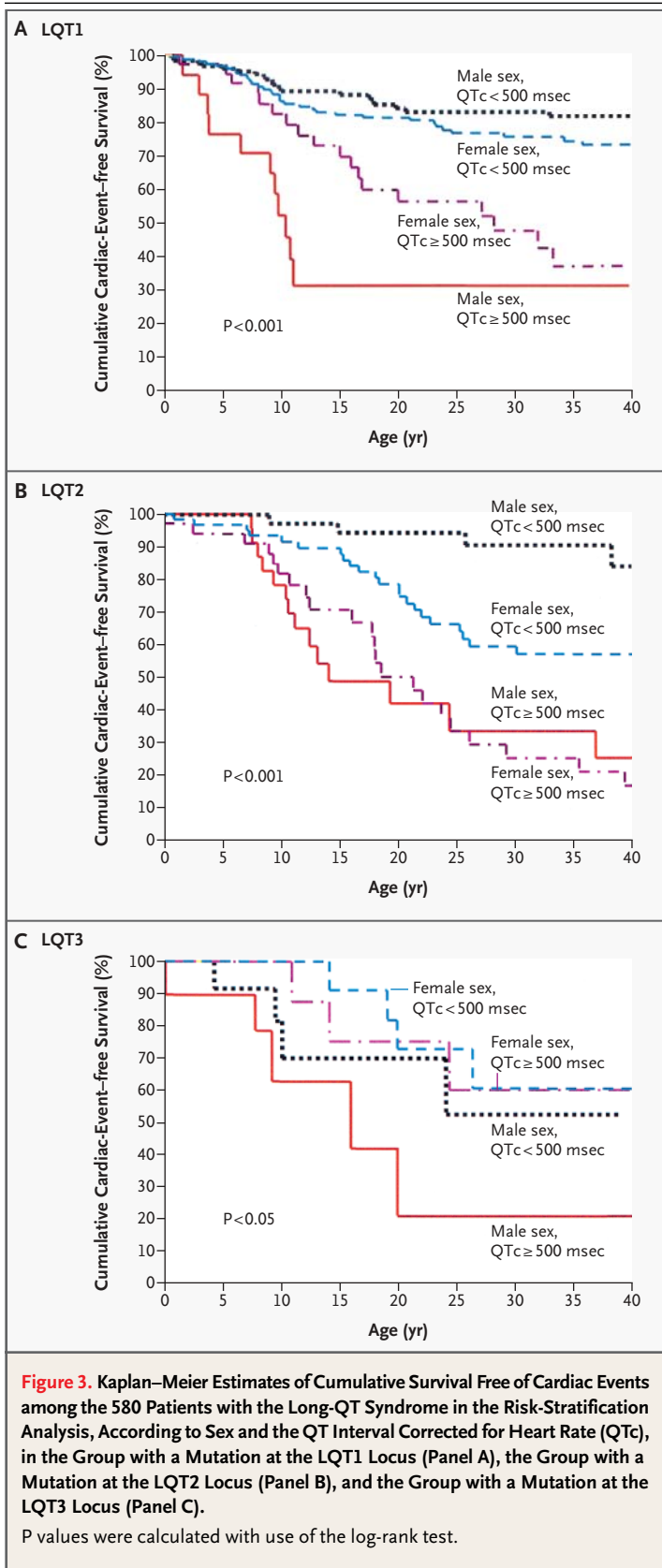
To assess the significance and independence of the predictors of the occurrence of a first cardiac event before the age of 40 years and before therapy, we entered the genetic locus, sex, and QTc in a Cox regression model. The analysis showed that both QTc ($P < 0.001$) and genetic locus ($P = 0.005$), but not sex, were independent predictors of a first cardiac event.

Patients with a mutation at the LQT1 locus were at the lowest risk for a first cardiac event before the age of 40 years and before therapy; thus, a substantial proportion of such patients remain asymptomatic. As compared with patients with a mutation at the LQT1 locus, patients with a mutation at the LQT2 locus had a relative risk of a first cardiac event of 1.61 (95 percent confidence interval, 1.16 to 2.25) and those with a mutation at the LQT3 locus had a relative risk of 1.80 (95 percent confidence interval, 1.07 to 3.04). Among patients with a mutation at the LQT1 locus and patients with a mutation at the

LQT2 locus, those with a QTc in the third quartile (469 to 498 msec) had a risk of cardiac events that was increased by a factor of 5.34 (95 percent confidence interval, 2.82 to 10.13) and those with a QTc in the highest quartile (more than 498 msec) had a risk that was increased by a factor of 8.36 (95 percent confidence interval, 2.53 to 27.21), as compared with those with a QTc in the lowest quartile (446 msec or less; these patients were silent mutation carriers). By contrast, among patients with a mutation at the LQT3 locus, the QTc did not differentiate risk between the first and fourth quartiles, whereas male sex was associated with a significantly greater risk of such events than was female sex (relative risk, 2.76; 95 percent confidence interval, 1.01 to 7.51).

For a more detailed characterization of risk according to genotype among patients with the long-QT syndrome, we created 12 categories including, for each genetic locus, the four combinations of sex (male and female) and QTc (less than 500 msec and 500 msec or more). The cumulative rate of survival free of a first cardiac event before the age of 40 years and before therapy differed significantly among these categories, thus making possible the identification of a differential risk (Fig. 3). A QTc of 500 msec or more, present in 24 percent of this patient population, had the single most important role in predicting events; however, this factor was modulated by sex and genetic locus. Among patients with a mutation at the LQT1 locus and a QTc of 500 msec or more, the risk of a first event was not affected by increasing age among female patients, whereas for male patients the risk was extremely high during the first 10 years of life, when symptoms developed in 70 percent, but subsequently declined. Among patients with a mutation at the LQT2 locus, female sex carried an especially high risk, since even female patients with a QTc of less than 500 msec had a probability of becoming symptomatic that was four times as high as that of male patients with a similar QTc. Among patients with a mutation at the LQT3 locus, male patients became symptomatic much earlier than female patients even when their QTc was below 500 msec (however, caution is required in drawing conclusions from this group given its relatively small size). Ranking the cumulative probability of a first cardiac event before the age of 40 years and before therapy yielded a risk-stratification scheme that may guide therapeutic strategies in patients with the long-QT syndrome whose genotypes had been determined (Fig. 4).

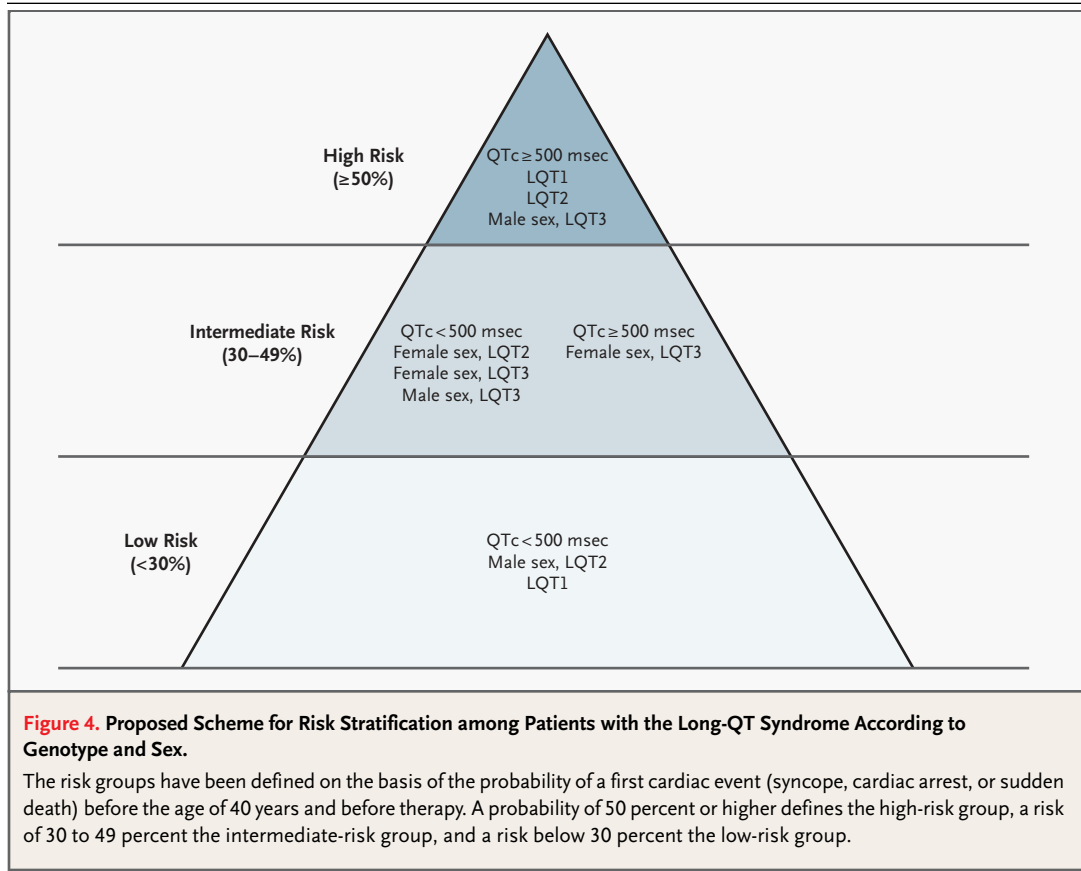
DISCUSSION



This study provides two main insights relevant for the management of the long-QT syndrome. By investigating our large data base of unselected, consecutively genotyped patients and by analyzing the incidence of cardiac events before the initiation of therapy, we were able to characterize the natural history of the syndrome according to the genetic locus. By using two clinical features (sex and QTc) in addition to the genetic locus, we developed a tool for gene-specific risk stratification with possible implications for disease management.

The efforts of the International Registry for Long QT Syndrome¹³ have proved the most successful to date in defining the natural history of the syndrome and identifying risk factors. In 1985, Moss et al. suggested an association between phenotypic and demographic features (congenital deafness, female sex, and a history of syncope or ventricular tachyarrhythmias) and cardiac events by analyzing data from 196 patients, of whom only 25 percent had a history of syncope.¹⁴ In 1991, Moss et al. used records from 328 families of unknown genotype to demonstrate the link between QTc and the risk of cardiac events.¹⁵ Zareba et al. subsequently examined the influence of genotype on the clinical course of the long-QT syndrome and found that the risk of cardiac events was higher among patients with a mutation at the LQT1 locus and those with a mutation at the LQT2 locus than among those with a mutation at the LQT3 locus, whereas the percentage of lethal cardiac events was highest among patients with a mutation at the LQT3 locus.⁸ However, this study was potentially biased, since it included only 38 families (selected because they were large enough to permit linkage analysis). We have further analyzed risk in patients with the long-QT syndrome by studying a large number of patients of known genotype from consecutive and unselected families.

The high potential of the long-QT syndrome to cause lethal events is demonstrated by the 13 percent incidence of cardiac arrest or sudden death among untreated patients. At variance with earlier observations,⁸ we found that the incidence of life-threatening events was lowest among patients with a mutation at the LQT1 locus. Sex affected the probability of a first cardiac event: the risk of becoming symptomatic before the age of 40 years and before therapy was higher among female than male patients with a mutation at the LQT2 locus and among male than female patients with a mutation at the



LQT3 locus, whereas there was no significant difference between the sexes among patients with a mutation at the LQT1 locus. Interestingly, cardiac events occurred earlier in male patients with a mutation at the LQT1 locus or with a mutation at the LQT2 locus than in female patients, whereas we found no sex-based difference in the age at onset of symptoms among patients with a mutation at the LQT3 locus. However, caution is required in interpreting data in the LQT3 subgroup because of its small size.

We found that the QT interval is influenced by the genetic locus and correlates significantly with the likelihood of cardiac events. The robustness of the latter finding relied on the use of QTc quartiles derived from both the entire population and the specific genetic variants. The prevalence of silent mutation carriers (carriers with a normal QTc) varied according to the genetic locus and was the highest among patients with a mutation at the LQT1 locus (36 percent). Therefore, it could be hazardous to assume that a member of a family with a

mutation at the LQT1 locus who has a normal QTc is not affected.¹² By contrast, this risk is small in a member of a family with a mutation at the LQT3 locus, since only few carriers (10 percent) in this group have a normal QTc.

We developed a risk-stratification model in order to quantify, for each genetic variant, the risk of symptoms before the age of 40 years and before therapy on the basis of two simple clinical characteristics: sex and QTc. Analysis of QTc revealed that only the highest quartile (QTc more than 498 msec) was associated with a markedly increased probability of cardiac events. Therefore, we used 500 msec as the cutoff point for categorical risk stratification. To quantify the probability of a first cardiac event before the age of 40 years, we categorized patients according to the genetic locus, and within each genetic variant, we identified four groups: male patients with a QTc of less than 500 msec, female patients with a QTc of less than 500 msec, male patients with a QTc of 500 msec or more, and female patients with a QTc of 500 msec or more.

The risk of events among patients with a mutation at the LQT1 locus was strongly dependent on the duration of QTc: male patients with a QTc of 500 msec or more were at high risk for a first cardiac event during childhood, whereas the risk of a first event among female patients with a mutation at the LQT1 locus who had a QTc of 500 msec or more was unchanged over time. Patients of either sex with a mutation at the LQT1 locus who had a QTc of less than 500 msec had a risk of a first cardiac event before the age of 40 years of less than 30 percent. Female patients with a mutation at the LQT2 locus had a more severe prognosis irrespective of the duration of the QTc, whereas in patients with a mutation at the LQT3 locus, the prognosis was mainly influenced by sex: male patients had a higher probability of becoming symptomatic by the age of 40 years than did female patients.

Our data make possible a revision of previous recommendations for risk stratification¹⁶ and the management of asymptomatic long-QT syndrome whenever information on genotype is available. Although an assessment of the efficacy of prophylactic therapy with beta-blockers¹⁷ is clearly beyond the scope of our present study, it is reasonable to assume, on the basis of our findings, that prophylactic treatment is warranted in male and female patients with a mutation at the LQT1 locus who have a QTc of 500 msec or more, male patients with a mutation at the LQT2 locus who have a QTc of 500 msec or more, all female patients with a mutation at the LQT2 locus irrespective of the QTc, and all patients with a mutation at the LQT3 locus. By con-

trast, the decision to institute therapy in patients at lower risk of becoming symptomatic before the age of 40 years should be individualized. Our risk-stratification scheme will help physicians assess the risk-benefit ratio of long-term therapy in their asymptomatic patients.

Our study was based on the assumption that patients with the long-QT syndrome who have mutations at the same locus have a similar risk of cardiac events. Should preliminary evidence that specific mutations are more malignant than others^{18,19} be confirmed, it might become possible to develop locus-specific risk-stratification schemes based either on specific mutations or on their functional effects.

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