Long-QT Syndrome After Age 40

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Background—Previous studies that assessed the risk of life-threatening cardiac events in patients with congenital long-QT syndrome (LQTS) have focused mainly on the first 4 decades of life, whereas the clinical course of this inherited cardiac disorder in the older population has not been studied.

Methods and Results—The risk of aborted cardiac arrest or death from age 41 though 75 years was assessed in 2759 subjects from the International LQTS Registry, categorized into electrocardiographically affected (corrected QT interval [QTc] ≥470 ms), borderline (QTc 440 to 469 ms), and unaffected (QTc <440 ms) subgroups. The affected versus unaffected adjusted hazard ratio for aborted cardiac arrest or death was 2.65 (P<0.001) in the age range of 41 to 60 years and 1.23 (P=0.31) in the age range of 61 to 75 years. The clinical course of study subjects displayed gender differences: AFFECTED LQTS women experienced a significantly higher cumulative event rate (26%) than borderline (16%) and unaffected (12%) women (P=0.001), whereas event rates were similar among the 3 respective subgroups of men (29%, 26%, and 27%; P=0.16). Recent syncope (<2 years in the past) was the predominant risk factor in affected subjects (hazard ratio 9.92, P<0.001), and the LQT3 genotype was identified as the most powerful predictor of outcome in a subset of 871 study subjects who were genetically tested for a known LQTS mutation (hazard ratio 4.76, P=0.02).

Conclusions—LQTS subjects maintain a high risk for life-threatening cardiac events after age 40 years. The phenotypic expression of affected subjects is influenced by age-specific factors related to gender, clinical history, and the LQTS genotype. (Circulation. 2008;117:2192-2201.)

Key Words: long-QT syndrome ■ risk factors ■ mortality

The congenital long-QT syndrome (LQTS) is caused by mutations that encode cardiac ion channel proteins which regulate the flux of sodium, potassium, and calcium ions across myocellular membranes, resulting in prolonged ventricular repolarization and an increased risk for sustained ventricular tachyarrhythmias.1 These genetic disorders are associated with sudden cardiac death in young individuals without structural heart disease.2 It has been shown that the phenotypic expression of LQTS is not uniform because of variable penetrance and that it is influenced by age, gender, genotype, environmental factors, therapy, and possibly other modifier genes.3–13 These data, however, were analyzed in studies that have assessed the clinical course of affected subjects during the first 4 decades of life, whereas the independent contribution of LQTS to the risk of life-threatening cardiac events after the age of 40 years has not been studied. It has been suggested that subjects who are affected with this congenital genetic disorder and survive to age 40 have a relatively lower risk of experiencing LQTS-related fatal or near-fatal arrhythmic events than their younger counterparts. It is also possible that the increasing prevalence of other forms of cardiac and noncardiac acquired disease processes may dominate mortality risk in the older age group.

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Clinical Perspective p 2201

The International LQTS Registry has recently expanded the duration of follow-up for enrolled subjects. Using these

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updated data, we performed a comprehensive analysis of the clinical course of LQTS patients beyond the age of 40 years.

Methods

Study Population

The study population was drawn from the International LQTS Registry and involved enrolled LQTS subjects and their unaffected family members who were followed up after the age of 40 years. The first member of a family to be identified with LQTS, the proband, was usually brought to medical attention because of a syncopal episode during childhood or teenage years. Subjects were excluded from the analysis if they were more than second-degree relatives of probands and did not undergo genetic testing, owing to a lack of complete information in the registry about the clinical course of nongenotyped distant relatives of probands. The final study population comprised 2759 subjects from 779 proband-identified families.

Data Collection and Management

Among the 2759 study patients, the mean ± SD age at enrollment in the registry was 45.3 ± 14.5 years (median 43.0 years, interquartile range 25.0 to 61.0 years). On enrollment, a complete past medical history was obtained to the enrolled age, and ongoing clinical information was obtained at yearly intervals thereafter. The mean ± SD follow-up time after age 40 for study subjects was 19.0 ± 13.5 years (median 15.9 years, interquartile range 7.7 to 29.6 years).

Clinical data were recorded on prospectively designed forms and included individual and family history and demographic, ECG, therapeutic, and cardiac event information. On enrollment in the International LQTS Registry, a 12-lead ECG was obtained from each subject as described previously. From this first recorded ECG, the duration of the QT interval was assessed from lead II (or lead I or III if the QT interval could not be measured from lead II) and corrected for heart rate (QTc) by use of Bazett’s formula. Additional serial QTc recordings were obtained from ECGs recorded during follow-up contacts, usually at yearly intervals. Follow-up data on β-blocker therapy included the starting date, type of β-blocker, and discontinuation date, if any. Among subjects who died, the use of a β-blocker before death was determined retrospectively. Information on other LQTS-related therapies (eg, implantable cardioverter defibrillator [ICD], left cervical sympathetic denervation, and pacemaker implantation) was also recorded prospectively.

Since January 2004, the International LQTS Registry has obtained follow-up data on non-LQTS comorbidities for enrolled subjects who are >40 years old. Data on acquired comorbidities are obtained through baseline and follow-up questionnaires that are sent at the yearly follow-up assessment to enrolled subjects in the >40 age group. Current information on the frequency of acquired comorbidities after the age of 40 years in registry patients is reported in the present study.

Genetic testing for a mutation that previously had been described as causing LQTS (in the LQTS genes CACNA1c, HERG, KCNE1, KCNE2, KCNJ2, KVLQT1, MIRP1, RYR2, and SCN5A) was performed in 871 study patients from 275 proband-identified families. A total of 539 genotyped subjects (62%) were identified as carriers of an LQTS mutation and were thus categorized as genotype positive (77% of genotype-negative patients were tested only for the mutation that was identified in their family). The LQTS genotype was determined with standard mutational analytic techniques that involved 5 established genetic laboratories associated with the International LQTS Registry.

All subjects provided informed consent, in which they agreed to inclusion in the registry and subsequent clinical studies. The study was approved by the University of Rochester Medical Center Institutional Review Board.

Study Groups and Outcome Measures

The primary objective of the present study was to evaluate whether congenital LQTS contributes to the risk of fatal or near-fatal events after the fourth decade of life beyond the risk conferred by acquired disease processes during this time period in the unaffected population. In the older age group, it is difficult in many cases to distinguish LQTS-related fatal events from those that occur as a result of other acquired cardiac and noncardiac disorders. Furthermore, the mode of death in registry subjects was not established by an end-point committee. Therefore, in contrast to previous LQTS studies in younger age groups that evaluated a specific end point composed of LQTS-related cardiac events, the primary end point of the present study was a first occurrence of aborted cardiac arrest (ACA) due to any cause (which required external defibrillation as part of the resuscitation) or death due to any cause from age 41 through 75 years.

Enrolled subjects were categorized into 3 prespecified subgroups that included (1) electrocardiographically affected LQTS subjects (QTc ≥ 470 ms), (2) borderline subjects (QTc 440 to 469 ms), and (3) unaffected subjects (QTc < 440 ms). To minimize the influence of an age-related increase in QTc duration, the ECG presence of LQTS was based on the maximum QTc duration that was recorded before age 40 years or on the first recorded ECG after age 40 in patients without prior ECG data. In addition, all outcome analyses were repeated in the subgroup that consisted of the 871 subjects who were tested genetically for a known LQTS mutation. In that analysis, the clinical course of genotype-positive subjects was compared with that of genotype-negative individuals.

Statistical Analysis

The clinical characteristics of study subjects among the 3 QTc categories were compared with the χ² test and Fisher exact test for categorical variables and the t test or Mann-Whitney-Wilcoxon test for continuous variables. The Kaplan-Meier estimator was used to assess the time to a first life-threatening event and the cumulative event rates by QTc subgroups and LQTS genotypes. Subgroups were compared with the log-rank statistic.

Multivariable Cox proportional hazards regression modeling was used to assess the independent contribution of each factor to the development of ACA or death from age 41 through 75 years. To account for potential nonproportional hazards during this relatively long follow-up period in which gender-related changes in mortality risk are known to occur, follow-up was separated into 2 prespecified age groups: 41 through 60 years and 61 through 75 years.

Predictors of ACA or death were assessed in the following groups: (1) all subjects (n = 2759); (2) separately in affected (n = 924), borderline (n = 754), and unaffected (n = 1081) subjects; (3) all genotyped subjects (n = 871); and (4) genotype-positive subjects only (n = 539). Prespecified factors in the all-subjects models included ECG presence of LQTS (defined by the prespecified QTc categories), gender, and a history of prior syncope (defined as transient loss of consciousness that was abrupt in onset and offset). The occurrence of syncope was evaluated in a time-dependent manner and was further categorized as a recent event (<2 years) or as more distant events (2 to 10 years or >10 years) to evaluate the independent contribution of the timing of non-life-threatening cardiac events to the development of fatal or near-fatal events after age 40. In the separate analyses that were performed within the subgroups of affected, borderline, and unaffected subjects, QTc duration was dichotomized at the upper quartile of each respective subgroup. Further adjustments for genetic data were included in the genotype-affected models. In the models that included all genotyped subjects, genotype-negative subjects formed the reference group to genotype-positive subjects and to the individual LQT1, LQT2, and LQT3 genotypes; in the models that included only genotype-positive subjects, the LQT1 genotype formed the reference group to LQT2 and LQT3. To further validate the risk associated with LQTS genotypes, we performed an alternative analysis in which genotype-negative patients who were phenotypically affected (eg, with QTc ≥ 470 ms) were excluded from the reference group of the genotyped models.
All models were further assessed for the effect of time-dependent \beta-blocker therapy on outcome. Because \beta-blockers were administered at the discretion of each subject’s attending physician to those considered to be at high risk, the efficacy of this mode of medical therapy was evaluated within identified risk group categories.

Of the 779 families included in the study, no family had 3 or more observed end-point events, 11 families had 2 events, 88 families had 1 event, and 680 families were event free in the age range of 41 to 60 years. Similarly, in the age range of 61 to 75 years, 12 families had 2 events, and 115 families had 1 event. We therefore did not attempt to adjust for family membership, because its potential impact would have to be very limited and only weakly identifiable (essentially based on just 11 or 12 families). Grouped jackknife estimates of SEs were compared with the standard large-sample estimates to verify this claim.16

The statistical software used for the analyses was SAS version 9.1.3 (SAS Institute Inc, Cary, NC). A 2-sided 0.05 significance level was used for hypothesis testing.

The authors had full access to and take full responsibility for the integrity if the data. All authors have read and agree to the manuscript as written.

Results

The clinical characteristics and the frequency of non–LQTS-related comorbidities by QTc category are shown in Tables 1 and 2, respectively. Affected and borderline LQTS subjects in the upper 2 QTc categories displayed a higher proportion of women and family history of sudden cardiac death than unaffected subjects in the lower QTc category (Table 1). Complete information on comorbidities was obtained for 1273 study subjects (46%; Table 2). The mean±SD age at which the last follow-up questionnaire was completed was 60±13 years: 462 patients completed the questionnaire once, 371 completed it twice, and 440 patients had follow-up data on comorbidities for 3 years. Among subjects for whom data on comorbidities were available, no significant differences were shown among the 3 QTc categories with regard to the frequency of acquired cardiovascular, cerebrovascular, and pulmonary disorders in the 2 age groups that were assessed. In addition, the frequency of cigarette smoking and smoking dose were similar among QTc categories (Table 2).

Clinical Course of Study Subjects After Age 40 Years

Total Population

The frequency of LQTS-related therapies and cardiac events during follow-up displayed a direct correlation with increasing QTc categories (Table 3). Accordingly, the cumulative probability of a fatal or near-fatal event at age 75 years was significantly higher among affected subjects (28%) than among borderline or unaffected subjects (20% and 21%, respectively, \(P=0.02\); Figure 1). The difference in the rate of ACA or death among QTc categories was most prominent during the first 20 years of follow-up after age 40 years and was attenuated thereafter. Thus, in multivariable analysis (Table 4), the adjusted risk of ACA or death for affected versus unaffected subjects was 2.65 (\(P<0.001\)) in the age range of 41 to 60 years and 1.23 (\(P=0.31\)) in the age range of 61 to 75 years.

Table 1. Characteristics of Study Patients by ECG Presence of LQTS (QTc Categorization):

<table>
<thead>
<tr>
<th>QTc Category</th>
<th>Unaffected: (&lt;440 \text{ ms} (n=1081))</th>
<th>Borderline: (440–469 \text{ ms} (n=754))</th>
<th>Affected: (\geq470 \text{ ms} (n=924))</th>
</tr>
</thead>
</table>

### Clinical history

- **Women, n (%):**
  - Unaffected: 483 (45)
  - Borderline: 467 (62)
  - Affected: 664 (72)*

- **Family history of SCD, n (%):**
  - Unaffected: 91 (8)
  - Borderline: 85 (11)
  - Affected: 123 (13)*

### ECG data†

- **QTc, median (IQ range):**
  - Unaffected: 410 (400–420)
  - Borderline: 450 (440–460)
  - Affected: 500 (480–530)

- **RR, median (IQ range):**
  - Unaffected: 920 (820–1040)
  - Borderline: 840 (760–970)
  - Affected: 865 (750–1000)*

- **QRS, median (IQ range):**
  - Unaffected: 80 (80–90)
  - Borderline: 80 (80–90)
  - Affected: 80 (80–90)

- **PR, median (IQ range):**
  - Unaffected: 160 (140–180)
  - Borderline: 160 (140–180)
  - Affected: 160 (140–180)

### Genotyped subjects

- **Positive, n (%):**
  - Unaffected: 62 (6)
  - Borderline: 128 (17)
  - Affected: 349 (38)*

- **LQT1, n (% of genotyped +):**
  - Unaffected: 35 (56)
  - Borderline: 70 (55)
  - Affected: 172 (49)

- **LQT2, n (% of genotyped +):**
  - Unaffected: 21 (34)
  - Borderline: 48 (38)
  - Affected: 134 (38)

- **LQT3, n (% of genotyped +):**
  - Unaffected: 4 (6)
  - Borderline: 7 (5)
  - Affected: 35 (10)

- **Other mutations, n (%):**
  - Unaffected: 2 (3)
  - Borderline: 3 (2)
  - Affected: 8 (2)

- **Double mutations, n (%):**
  - Unaffected: 1 (2)
  - Borderline: 1 (1)
  - Affected: 7 (2)

- **Negative, n (%):**
  - Unaffected: 202 (77)
  - Borderline: 93 (42)
  - Affected: 37 (10)

SCD indicates sudden cardiac death; IQ, interquartile.

*\(P<0.05\) for comparison among the 3 QTc categories.

†Data were obtained from the ECG with the maximum QTc value recorded before age 40 years or from the first recorded ECG after age 40 years in patients without prior ECG data.

‡Genotype-negative subjects were not uniformly tested for all known LQTS mutations (e.g. some were tested only for the mutation known in their families).
Age group 61–75 y, n 200 147 153
respectively; differences in the rate of ACA or death (Figure 2A and 2B): At age 75 years, the cumulative probability of ACA or death displayed relatively high cumulative event rates that were similar among the affected, borderline, and unaffected subgroups (29%, 26%, and 27%, respectively; \( P=0.16 \); Figure 2B). Consistently, when gender effect was examined within

<table>
<thead>
<tr>
<th>Table 2. Characteristics of Study Patients by ECG Presence of LQTS (QTc Categorization): Non–LQTS-related Comorbidities*</th>
<th>QTc Category</th>
<th>Unaffected: &lt;440 ms</th>
<th>Borderline: 440–469 ms</th>
<th>Affected: ≥470 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group 41–60 y, n</td>
<td>294</td>
<td>199</td>
<td>280</td>
<td></td>
</tr>
<tr>
<td>Age at questionnaire, y (mean±SD)†</td>
<td>51±5</td>
<td>51±5</td>
<td>50±6†</td>
<td></td>
</tr>
<tr>
<td>Smoking, n (%)$§</td>
<td>236 (48)</td>
<td>156 (52)</td>
<td>173 (60)</td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)‡</td>
<td>94 (47)</td>
<td>77 (52)</td>
<td>82 (56)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>21 (11)</td>
<td>21 (14)</td>
<td>16 (10)</td>
<td></td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td>19 (10)</td>
<td>18 (13)</td>
<td>22 (14)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>14 (7)</td>
<td>15 (10)</td>
<td>16 (9)</td>
<td></td>
</tr>
<tr>
<td>Coronary angiography/angioplasty, n (%)</td>
<td>19 (10)</td>
<td>13 (9)</td>
<td>21 (14)</td>
<td></td>
</tr>
<tr>
<td>CABC, n (%)</td>
<td>9 (5)</td>
<td>10 (7)</td>
<td>13 (9)</td>
<td></td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>13 (7)</td>
<td>10 (7)</td>
<td>16 (9)</td>
<td></td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>10 (10)</td>
<td>22 (13)</td>
<td>25 (10)</td>
<td></td>
</tr>
<tr>
<td>Menopause, n (% of females)</td>
<td>97 (100)</td>
<td>86 (100)</td>
<td>113 (100)</td>
<td></td>
</tr>
<tr>
<td>Menopause age, y (mean±SD)</td>
<td>47±7</td>
<td>48±6</td>
<td>48±6</td>
<td></td>
</tr>
</tbody>
</table>

CABC indicates coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease.

*Data on comorbidities were obtained from a questionnaire that was filled out by 1273 study subjects.
†Indicates mean age of study subjects at which the last (most updated) data regarding comorbidities were obtained from yearly follow-up questionnaires.
‡For comparison among the 3 QTc categories \(<0.05\).
§After age 41 years, only a small number of patients started to smoke; therefore, all smokers are reported together.

The clinical course of affected, borderline, and unaffected subjects after 40 years of age displayed important gender differences in the rate of ACA or death (Figure 2A and 2B): At age 75 years, the cumulative probability of ACA or death was significantly higher among affected LQTS women (26%) than among borderline and unaffected women (16% and 12%, respectively; \( P=0.001 \); Figure 2A), whereas male subjects displayed relatively high cumulative event rates that were similar among the affected, borderline, and unaffected subgroups (29%, 26%, and 27%, respectively; \( P=0.16 \); Figure 2B). Consistently, when gender effect was examined within

<table>
<thead>
<tr>
<th>Table 3. Clinical Course of Study Subjects by the ECG Presence of LQTS (QTc Categorization)</th>
<th>QTc Category</th>
<th>Unaffected: &lt;440 ms</th>
<th>Borderline: 440–469 ms</th>
<th>Affected: ≥470 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before age 41 y</td>
<td>Treatment, n (%)</td>
<td>β-Blocker therapy 38 (4)</td>
<td>56 (7)</td>
<td>248 (27)*</td>
</tr>
<tr>
<td></td>
<td>LCSD</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)*</td>
</tr>
<tr>
<td></td>
<td>Pacemaker</td>
<td>1 (0)</td>
<td>2 (0)</td>
<td>39 (4)*</td>
</tr>
<tr>
<td></td>
<td>ICD</td>
<td>0 (0)</td>
<td>5 (1)</td>
<td>45 (5)*</td>
</tr>
<tr>
<td></td>
<td>Events, n (%)</td>
<td>Syncope 101 (9)</td>
<td>103 (14)</td>
<td>318 (34)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACA</td>
<td>1 (0.1)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Ages 41–75 y</td>
<td>Treatment, n (%)</td>
<td>β-Blocker therapy 169 (16)</td>
<td>214 (29)</td>
<td>479 (53)*</td>
</tr>
<tr>
<td></td>
<td>LCSD</td>
<td>0 (0)</td>
<td>1 (0.1)</td>
<td>7 (0.8)*</td>
</tr>
<tr>
<td></td>
<td>Pacemaker</td>
<td>16 (3)</td>
<td>20 (3)</td>
<td>41 (4)*</td>
</tr>
<tr>
<td></td>
<td>ICD</td>
<td>11 (1)</td>
<td>27 (4)</td>
<td>101 (11)*</td>
</tr>
<tr>
<td></td>
<td>Events, n (%)</td>
<td>Syncope 48 (5)</td>
<td>67 (9)</td>
<td>157 (17)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACA</td>
<td>5 (0.5)</td>
<td>9 (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Death</td>
<td>72 (7)</td>
<td>58 (8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACA or death</td>
<td>75 (7)</td>
<td>62 (8)</td>
</tr>
</tbody>
</table>

LCSD indicates left cervical sympathetic denervation; ICD, implantable cardioverter defibrillator.

*\( P<0.05 \) for comparison among the 3 QTc categories.

QTc categories (Figure 3), unaffected men had a significantly higher risk of ACA or death after 60 years of age than unaffected women (Figure 3), whereas among affected LQTS subjects, gender risk was similar throughout follow-up (Figure 3; Table 5). These findings suggest that the higher male risk related to acquired cardiovascular disorders in the unaffected population is counterbalanced in the affected population by a higher female risk related to the genetic disorder, which leads to a similar risk of fatal or near-fatal events in LQTS men and women after age 40.

A history of time-dependent syncope was a powerful predictor of subsequent ACA or death in affected LQTS subjects (Table 5). In the age range of 41 to 60 years, the risk associated with syncope was highest when it occurred within the past 2 years during follow-up and intermediate when it occurred in the past 2 to 10 years, whereas in the older age group, syncope in the past 2 to 10 years had a significant effect on outcome. Syncope that occurred >10 years in the past was not a risk factor in either age group.

Among affected subjects, upper-quartile QTc durations (≥530 ms) were associated with a marginally significant \( (P=0.06) \) 68% increase in the risk of ACA or death in the age group of 41 to 60 years, whereas after this time period, the risk associated with a prolonged QTc duration was attenuated (Table 5). By contrast, upper-quartile QTc durations were not
associated with an increase in the risk of ACA or death in the unaffected or borderline subgroups (data not shown).

**Genotyped Population**
Among the 871 study subjects who were genetically tested for a known LQTS mutation, the cumulative probability of ACA or death at age 75 years was significantly higher among the 539 genotype-positive subjects (20%) than the 332 genotype-negative subjects (10%; \(P=0.002\); Figure 4A). The rate of fatal or near-fatal events was highest among carriers of the LQT3 genotype (35%) and intermediate among LQT2 genotype carriers (24%), whereas carriers of the LQT1 genotype exhibited the lowest event rate (14%), which was similar to the rate observed among genotype-negative subjects (10%; \(P=0.001\) for the comparison among the 4 genotyped subgroups; Figure 4B).

In multivariable analysis (Table 6), genotype-positive subjects had nearly a 4-fold increase in the risk of ACA or death compared with genotype-negative subjects in the age range of 41 through 60 years. LQT3 genotype carriers maintained the highest risk in this age group and had nearly a 5-fold increase in the risk of the end point compared with genotype-negative subjects, whereas LQT2 subjects had a marginally significant 2.5-fold increase in risk. By contrast, the risk for LQT1 genotype carriers was virtually identical to that for genotype-negative subjects (hazard ratio 1.01, \(P=0.99\)). Consistently, from age 41 through 60 years, LQT3 genotype carriers exhibited a 4.5-fold increase in the risk of ACA or death compared with carriers of the LQT1 genotype (Table 7). After this time period, the lack of a significant genotype effect may be related to the overall attenuation of the risk associated with LQTS in the older age group or to the relatively small number of LQT3 subjects who survived to follow-up after age 60 years (Figure 4B). The risk associated with each LQTS genotype was similar when patients who were treated with \(\beta\)-blockers were excluded from the analysis.

Notably, in the models that included genotyped patients, being the carrier of the LQT3 genotype was the most powerful predictor of outcome in the age range of 41 to 60 years, whereas clinical factors, including gender, QTc duration, and a history of prior syncope, did not maintain their significance as predictors of outcome after adjustment for genetic data. Furthermore, virtually identical results were obtained when genotype-negative patients who were electrocardiographically affected (QTc \(\geq 470\) ms) were excluded from the genotyped models. The grouped jackknife estimates of SEs (data not shown) averaged within 1.5% of the standard working-independence large-sample estimates, with approximately half increasing and half decreasing, which indicates that

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**Table 4. Multivariable Analysis: Predictors of ACA or Death After Age 40 Years: Risk in Total Population by ECG Presence of LQTS**

<table>
<thead>
<tr>
<th>ECG Categorization (QTc Duration)</th>
<th>Age Group 41–60 y ((n=2759))</th>
<th>Age Group 61–75 y ((n=1132))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>(P)</td>
</tr>
<tr>
<td>Affected ((\geq 470) ms) vs unaffected ((&lt; 440) ms)</td>
<td>2.65 (1.63–4.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Affected ((\geq 470) ms) vs borderline (440–469 ms)</td>
<td>1.36 (0.78–2.37)</td>
<td>0.28</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval.
*Findings were adjusted for the following additional covariates: gender, time-dependent syncope \(>2\) years, and time-dependent syncope \(>10\) years. The risk associated with prior syncope \(>10\) years and no syncope at any time were virtually identical; therefore, these 2 categories were collapsed to form the reference group. Similar findings were obtained after further adjustment for time-dependent \(\beta\)-blocker therapy.
the impact of potential dependencies due to family membership was indeed negligible, likely owing to the relatively small number of families with multiple observed events.

**β-Blocker and ICD Therapy After Age 40 Years**

Overall, 864 study subjects (31%) were treated with β-blocker therapy after 40 years of age, and the frequency of treatment with this mode of medical therapy was significantly higher in affected subjects with QTc $\geq 470$ ms (Table 3). β-Blocker therapy was associated with a nonsignificant 42% reduction in the risk of ACA or death in the age range of 41 to 60 years (hazard ratio 0.58, 95% confidence interval 0.16 to 2.07, $P = 0.40$) and a marginally significant 86% reduction in the risk of ACA or death in the age range of 61 to 75 years (hazard ratio 0.14, 95% confidence interval 0.02 to 1.20, $P = 0.047$) in affected LQTS subjects who experienced syncope in the past 10 years.

An ICD was implanted in 166 study subjects (6%), of whom 62 experienced ACA before implantation. None of the subjects in whom an ICD was implanted experienced ACA after implantation during a relatively short mean±SD follow-up period of 3.5±3.4 years. The cumulative probability of death in implanted subjects was 1% at age 60 and 7% at age 75 years. In a subset of 80 ICD-treated subjects for whom interrogation data were collected after implantation, at least 1 episode of ICD discharge occurred in 19 subjects (24%) during the same follow-up period (appropriate discharge: 12 subjects [15%]; inappropriate discharge: 7 subjects [9%]). Notably, appropriate ICD discharge occurred in 11 (16%) of 68 affected subjects and in 1 (8%) of 12 borderline or unaffected subjects.

**Discussion**

The present study is the first to report on the clinical course of LQTS subjects after the fourth decade of life. We have...
shown that this inherited cardiac disorder continues to confer a high risk of life-threatening cardiac events after age 40 years that is associated with age-specific clinical and genetic factors. Electrocardiographically affected subjects who had a QTc interval duration >470 ms were shown to experience more than a 2-fold increase in the risk of ACA or death compared with unaffected subjects with QTc <440 ms in the age range of 41 to 60 years. Furthermore, genetically tested subjects who were found to be carriers of a known LQTS mutation had nearly a 4-fold increase in risk in the same age group compared with genotype-negative subjects. After age 60, the risk of ACA or death conferred by LQTS was attenuated, possibly owing to the increasing prevalence of acquired comorbidities that contribute to mortality risk in the older age group.

Clinical factors shown in the present study to affect the phenotypic expression of affected LQTS subjects after age 40 included gender, QTc duration, and a history of syncope in the prior 10 years. Previous studies have demonstrated that the clinical course of LQTS subjects is associated with age-specific gender differences in the risk. Men were shown to have a significantly higher event rate than women in the preadolescence period, with risk reversal in gender-related risk in the postadolescence period. A recent study from the International LQTS Registry has further shown that women with LQTS have nearly a 3-fold increase in the risk of ACA or sudden cardiac death compared with men from age 18 through 40 years. After age 40, the gender-related risk of fatal or near-fatal events is also influenced by acquired disease processes. Consistently, we have shown that among electrocardiographically unaffected subjects with QTc <440 ms, men had a significantly higher risk of fatal or near-fatal events after age 60 years. By contrast, among affected LQTS subjects, the risk of ACA or death was similar in men and women. Furthermore, affected LQTS women displayed a significantly higher cumulative probability of ACA or death than borderline and unaffected women, whereas event rates among affected men were not significantly different from those observed in the borderline and unaffected male subgroups. Thus, the higher arrhythmic risk of LQTS women after age 40 appears to counterbalance the increased male risk due to acquired cardiovascular disease processes in this age group.

Data from the International LQTS Registry have shown that the LQTS genotype influences the clinical course of

**Table 5. Multivariable Analysis: Predictors of ACA or Death After Age 40 Years: Risk Factors in Electrocardiographically Affected LQTS Subjects (QTc ≥470 ms)**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Age Group 41–60 y (n=924)</th>
<th>Age Group 61–75 y (n=336)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>QTc duration, ms†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 (QTc ≥530) vs Q1–3 (QTc &lt;530)</td>
<td>1.68 (0.97–2.91)</td>
<td>0.06</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female vs male</td>
<td>0.88 (0.49–1.56)</td>
<td>0.28</td>
</tr>
<tr>
<td>Time-dependent syncope‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent (&lt;2 y) vs &gt;10 y or no syncope</td>
<td>9.92 (4.99–19.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intermediate (2–10 y) vs &gt;10 y or no syncope</td>
<td>2.76 (1.35–5.63)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval.
*Similar findings were obtained after further adjustment for time-dependent β-blocker therapy.
†QTc duration was dichotomized in the clinically affected subgroup at the upper quartile.
‡The risk associated with prior syncope >10 years and no syncope at any time was virtually identical; therefore, these 2 categories were collapsed to form the reference group.
affected subjects. It has been suggested that despite a higher cardiac event rate among LQT1 and LQT2 subjects during the first 4 decades of life, the lethality of cardiac events in LQT3 genotype carriers is higher before age 40 years. The present data extend these observations and demonstrate that in genetically tested individuals, the LQT3 genotype is the most powerful predictor of fatal or near-fatal events after age 40. LQT3 genotype carriers exhibited nearly a 5-fold increase in the risk of ACA or death compared with genotype-negative subjects, whereas the LQT2 genotype was shown to be associated with intermediate risk, and the risk of LQT1 subjects was similar to that of genotype-negative subjects. Notably, QTc duration was not a significant predictor of outcome in the genotyped models, and the risk associated with each LQTS genotype did not change when genotype-negative patients with QTc ≥470 ms were excluded from the reference group. Thus, it appears that genetic testing for a known LQTS mutation should be an important component in risk stratification for life-threatening cardiac events even after age 40.

Possibly because of the nonrandomized nature of the present study and the fact that the broad end point comprised ACA or death due to any cause, we did not identify a significant effect of β-blocker therapy in the present study. Furthermore, the indications for β-blocker therapy in the older age group also may include a relatively high proportion of non-LQTS-related acquired cardiovascular comorbidities. However, we have shown that a subset of high-risk, clinically affected LQTS subjects who experienced syncope during the past 10 years derived a marginally significant benefit from this mode of medical therapy in the older age group. Thus, the present findings suggest that the benefit of β-blocker therapy in LQTS patients is maintained after age 40 years.
### Table 6. Multivariable Analysis: Predictors of ACA or Death After Age 40 Years Among the Total Genotyped Population†

<table>
<thead>
<tr>
<th>Genetic Categorization</th>
<th>Age Group 41−60 y (n=871)</th>
<th>Age Group 61−75 y (n=323)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Genotype positive vs genotype negative</td>
<td>3.79 (1.05−14.67)</td>
<td>0.04</td>
</tr>
<tr>
<td>LQT1 vs genotype negative</td>
<td>1.01 (0.26−3.98)</td>
<td>0.99</td>
</tr>
<tr>
<td>LQT2 vs genotype negative</td>
<td>2.66 (0.80−8.80)</td>
<td>0.10</td>
</tr>
<tr>
<td>LQT3 vs genotype negative</td>
<td>4.76 (1.24−18.26)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval.

†Comprises all study subjects who were genetically tested (both genotype positive and genotype negative); similar findings were obtained after geno-
type-negative subjects with QTc ≥470 ms were excluded from the analysis.

### Study Limitations

Data on comorbidities were obtained for 46% of study subjects and at a relatively early period in the group >40 years old, which precluded a comprehensive analysis of possible important interactions between genetic and acquired factors in the elderly population. However, the similar distribution of all comorbidities among the 3 QTc categories suggests that the significantly higher risk of ACA or death among clinically affected subjects with QTc ≥470 ms is independent of acquired disease processes. In addition, only 80 of the 166 ICD recipients had their device interrogated, which precluded a complete evaluation of differences in the rate of appropriate ICD discharge among the 3 comparison groups.

### Conclusions

We have recently performed an age-specific evaluation of the clinical course of LQTS subjects from the International LQTS Registry during the childhood, adolescence, and postadolescence (ages 18 through 40 years) periods. The present study completes this analysis and further demonstrates that the phenotypic expression of this genetic disorder is age-specific and time-dependent. The present data demon-


**CLINICAL PERSPECTIVE**

The congenital long-QT syndrome (LQTS) is associated with increased risk for ventricular tachyarrhythmias and sudden cardiac death in young individuals without structural heart disease. It is not known whether this inherited cardiac disorder is associated with increased risk in older patients, in whom comorbidities may dominate mortality risk. The present study is the first to report on the clinical course of LQTS patients after the age of 40 years. We demonstrate that affected LQTS patients have a >2.5-fold increase in the risk of aborted cardiac arrest or death compared with their unaffected counterparts. Risk factors for aborted cardiac arrest or death after age 40 in LQTS patients include female gender and time-dependent syncope, whereas among unaffected individuals in this age group, men are shown to have a higher risk of life-threatening cardiac events. Importantly, we show that the presence of the LQT3 genotype is a powerful risk factor in this age group and is associated with nearly a 5-fold increase in the risk of aborted cardiac arrest or death, whereas the rate of life-threatening cardiac events among individuals with the LQT1 genotype is similar to that of genotype-negative patients. The results of this study demonstrate that LQTS continues to confer increased risk after age 40 and further stress the importance of identifying age-specific genetic and clinical risk factors in patients who are affected with this genetic disorder.
Long-QT Syndrome After Age 40

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