Risk Factors for Aborted Cardiac Arrest and Sudden Cardiac Death in Children With the Congenital Long-QT Syndrome

Ilan Goldenberg, MD; Arthur J. Moss, MD; Derick R. Peterson, PhD; Scott McNitt, MS; Wojciech Zareba, MD, PhD; Mark L. Andrews, BBA; Jennifer L. Robinson, MS; Emanuela H. Locati, MD; Michael J. Ackerman, MD, PhD; Jesaia Benhorin, MD; Elizabeth S. Kaufman, MD; Carlo Napolitano, MD; Silvia G. Priori, MD, PhD; Ming Qi, MD; Peter J. Schwartz, MD; Jeffrey A. Towbin, MD; G. Michael Vincent, MD; Li Zhang, MD

Background—The congenital long-QT syndrome (LQTS) is an important cause of sudden cardiac death in children without structural heart disease. However, specific risk factors for life-threatening cardiac events in children with this genetic disorder have not been identified.

Methods and Results—Cox proportional-hazards regression modeling was used to identify risk factors for aborted cardiac arrest or sudden cardiac death in 3015 LQTS children from the International LQTS Registry who were followed up from 1 through 12 years of age. The cumulative probability of the combined end point was significantly higher in boys (5%) than in girls (1%; P<0.001). Risk factors for cardiac arrest or sudden cardiac death during childhood included corrected QT interval (QTc) duration >500 ms (hazard ratio [HR]; 2.72; 95% confidence interval [CI], 1.50 to 4.92; P=0.001) and prior syncope (recent syncope [<2 years]; HR, 6.16; 95% CI 3.41 to 11.15; P<0.001; remote syncope [≥2 years]; HR, 2.67; 95% CI, 1.22 to 5.85; P=0.01) in boys, whereas prior syncope was the only significant risk factor among girls (recent syncope: HR, 27.82; 95% CI, 9.72 to 79.60; P<0.001; remote syncope: HR, 12.04; 95% CI, 3.79 to 38.26; P<0.001). β-Blocker therapy was associated with a significant 53% reduction in the risk of cardiac arrest or sudden cardiac death (P=0.01).

Conclusions—LQTS boys experience a significantly higher rate of fatal or near-fatal cardiac events than girls during childhood. A QTc duration >500 ms and a history of prior syncope identify risk in boys, whereas prior syncope is the only significant risk factor among girls. β-Blocker therapy is associated with a significant reduction in the risk of life-threatening cardiac events during childhood. (Circulation. 2008;117:2184-2191.)

Key Words: death, sudden • long-QT syndrome • risk factors

The congenital long-QT syndrome (LQTS) is caused by mutations that encode channels that regulate sodium, potassium, and calcium currents and by a mutation in a cytoskeletal gene (ankyrin B) that affects sodium and calcium kinetics, resulting in prolonged ventricular repolarization and an increased risk for sustained ventricular tachyarrhythmias.1 The genetic disorder is an important cause of sudden cardiac death (SCD) in children without structural heart disease. However, the risk in affected patients is not uniform because of variable penetrance and is influenced by age, gender, genotype, environmental factors, therapy, and possibly other modifier genes.3 In recent years, numerous advances have been made in the identification of the genotype-phenotype relationship and risk factors for cardiac events in LQTS patients.4-11 These data, however, were assessed mostly in studies that have included syncope as the predominant component in a composite cardiac event end point.

Editorial p 2178
Clinical Perspective p 2191

We have recently described the clinical course of LQTS patients during the adolescent12 and postadolescent13 periods...
and have shown that risk factors in this genetic disorder are age dependent. However, to date, specific risk factors for life-threatening cardiac events in LQTS children have not been assessed.

The objectives of the present study were to evaluate the contribution of prespecified genetic and clinical factors to the development of aborted cardiac arrest (ACA) or SCD in LQTS children, to determine whether interactions among risk factors can be used to identify risk subsets in this population, and to assess the efficacy of β-blocker therapy for the prevention of fatal or near-fatal cardiac events during childhood within the identified risk groups.

Methods

Study Population

The study population, drawn from the International LQTS Registry, involved children from proband-identified families.4 Children >1 year of age were considered to have LQTS if the QT interval corrected for heart rate (QTc) assessed with Bazett’s formula14 was ≥450 ms or if they had a documented LQTS mutation by genetic testing. Children were excluded from the analysis if they had a QTc <450 ms on the baseline ECG without a genotype positive mutation, experienced ACA or death or were lost to follow-up before 1 year of age, or were more than second-degree relatives of probands because of lack of complete information in the registry on the clinical course of more distant relatives of probands.

The final study group comprised 3015 children from 1249 proband-identified families, of whom 875 subjects from 272 enrolled families underwent genetic testing and were identified as carriers of a known LQTS mutation. The LQTS genotype was determined with standard mutational analytic techniques involving 5 established genetic laboratories associated with the International LQTS Registry.

Data Collection and Management

Follow-up was closed on March 30, 2006. Those who had not reached their 13th birthday on that date were censored at the time of their last contact. Those who were lost to follow-up also were censored at the time of their last contact. Among the 3015 study patients, the mean±SD age at enrollment in the registry was 7.5±5.4 years. On enrollment, complete history was obtained from birth to their enrolled age, and ongoing clinical information was obtained at yearly intervals thereafter. In the present study, we assessed the clinical course of study patients from 1 through 12 years of age. Thus, follow-up time for each study patient comprised historical clinical information from 1 year of age to enrollment and prospective follow-up information from enrollment through 12 years of age if the patient had not otherwise been censored for any of the above reasons. For each patient, data on personal and family histories, cardiac events, and therapy were systematically recorded at enrollment and at each visit or medical contact. Clinical data, recorded on prospectively designed forms, included patient and family histories and demographic, ECG, therapeutic, and cardiac event information. Data on β-blocker therapy included the starting date, type of β-blocker, and discontinuation date if appropriate. After a fatal event, the use of a β-blocker before death was determined retrospectively. Among the 3015 study patients, 2 died of non-LQTS causes, 32 were lost to follow-up and censored at the time of their last contact, and 329 had reached their 13th birthday when follow-up was closed. All patients or their guardians provided informed consent agreeing to inclusion in the registry and subsequent clinical studies. The study was approved by the University of Rochester Medical Center Institutional Review Board.

End Point

The primary end point of the study was time to ACA (requiring external defibrillation as part of the resuscitation) or LQTS-related SCD (death abrupt in onset without evident cause if witnessed or death that was not explained by any other cause if it occurred in a nonwitnessed setting such as sleep), whichever occurred first, from 1 through 12 years of age.

Results

Study Population

The clinical characteristics of study patients by gender are shown in Table 1. Girls made up 63% of the patients and...
had a significantly longer QTc duration compared with boys, whereas other ECG parameters were similar in boys and girls.

Male patients exhibited a significantly higher proportion of all types of LQTS-related cardiac events during follow-up compared with female patients and accordingly received a higher proportion of medical and nonmedical therapies for the genetic disorder (Table 2).

Genotyped patients had a gender distribution (Table 1) and a mean QTc duration (490 ± 54 ms) that were similar to those of the total population. However, patients who underwent genetic testing displayed several important clinical differences compared with nongenotyped individuals, including a lower frequency of probands (31% versus 45%, respectively; \( P < 0.001 \)), a higher frequency of SCD in affected family members (9% versus 4%, respectively; \( P < 0.001 \)), and a higher frequency of therapy with \( \beta \)-blockers during follow-up (22% versus 18%, respectively; \( P = 0.006 \)). Accordingly, the subset of study patients who were genotyped experienced a relatively low rate of LQTS-related life-threatening cardiac events during childhood (ACA, 1.2%; SCD, 0.5%).
threatening cardiac events during childhood among study patients. Furthermore, the effect of each of these 3 clinical factors displayed important differences among risk subsets of LQTS children (Tables 3 and 4; the corresponding number of patients, follow-up time, and crude event rates for each risk subset are provided in the Appendix of the online-only Data Supplement). By contrast, a family history of SCD in a subset are provided in the Appendix of the online-only Data Supplement). By contrast, a family history of SCD in a subset are provided in the Appendix of the online-only Data Supplement). By contrast, a family history of SCD in a subset are provided in the Appendix of the online-only Data Supplement).

![Figure 1. Kaplan–Meier estimates of the probability of ACA or SCD by gender (values in parentheses are event rates).](image)

Table 3. Risk Factors for ACA or SCD During Childhood: Male Versus Female HR in Risk Subsets*

<table>
<thead>
<tr>
<th>Risk Subset</th>
<th>Male vs Female Risk</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prior syncope and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTc &gt;500 ms</td>
<td></td>
<td>12.11 (3.73–39.31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QTc ≤500 ms</td>
<td></td>
<td>4.23 (1.47–12.19)</td>
<td>0.008</td>
</tr>
<tr>
<td>Prior syncope and</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTc &gt;500 ms</td>
<td></td>
<td>2.68 (1.22–5.91)</td>
<td>0.01</td>
</tr>
<tr>
<td>QTc ≤500 ms</td>
<td></td>
<td>0.94 (0.38–2.30)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

*Findings are derived from the main interaction model that was identified to have the best fit for the data. Covariates and interactions in the model included recent syncope (<2 years) versus no syncope, remote syncope (≥2 years) versus no syncope, QTc duration, gender, gender-by–prior syncope (at anytime during childhood) interaction, and gender-by–QTc interaction. See the supplementary Appendix for corresponding patient counts, follow-up time, events, and crude event rates in each risk subset.

Table 4. Risk Factors for ACA or SCD During Childhood: Risk Factors for Boys and Girls*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Males (HR (95% CI))</th>
<th>P</th>
<th>Females (HR (95% CI))</th>
<th>P</th>
<th>P for Interaction†</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.055</td>
</tr>
<tr>
<td>QTc &gt;500 ms vs ≤500 ms</td>
<td>2.72 (1.50–4.92)</td>
<td>0.001</td>
<td>0.95 (0.39–2.33)</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Prior syncope</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recent (&lt;2 y) vs no syncope</td>
<td>6.16 (3.41–11.15)</td>
<td>&lt;0.001</td>
<td>27.82 (9.72–79.60)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Remote (≥2 y) vs no syncope</td>
<td>2.67 (1.22–5.85)</td>
<td>0.01</td>
<td>12.04 (3.79–38.26)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Findings are derived from the main interaction model that was identified to have the best fit for the data. Covariates and interactions in the model included recent syncope (<2 years) versus no syncope, remote syncope (≥2 years) versus no syncope, QTc duration, gender, gender-by–prior syncope (at anytime during childhood) interaction, and gender-by–QTc interaction. See the online-only Data Supplement Appendix for corresponding patient counts, follow-up time, events, and crude event rates in each risk subset.

†Denotes the probability value for interaction between gender and each risk factor. The interaction terms for recent syncope by gender and remote syncope by gender were similar. Therefore, the interaction for any prior syncope by gender was included in the multivariable model.

‡Interaction terms for recent syncope by gender and remote syncope by gender were similar. Therefore, the interaction for any prior syncope by gender was included in the multivariable model.
The nature of time-dependent covariates precludes assessment of cumulative event rates based only on the covariate pattern at the time origin. Therefore, to obtain an estimate of event rates during childhood for patients who experienced syncope during follow-up, we identified time-independent risk groups at 6 years of age, stratified by the occurrence of syncope before 6 years of age, and evaluated the cumulative probability of ACA or SCD from 6 through 12 years of age (Figure 3). This analysis demonstrated that the rate of life-threatening events during childhood was highest among boys who experienced prior syncope (15%), intermediate in girls with a history of syncope and asymptomatic boys (4% and 3%, respectively), and lowest in girls without a history of prior syncope (0.6%; \(P<0.001\)).

**Genotyped Patients**

When predictors of life-threatening cardiac events were analyzed in the subgroup of LQTS children who were genotyped, clinical factors, including time-dependent syncope (HR, 4.23; 95% CI, 1.13 to 15.85; \(P=0.03\)) and male gender (HR, 5.05; 95% CI, 1.08 to 23.53; \(P=0.04\)), were identified as predictors of outcome, whereas nonsignificant differences in the risk for life-threatening cardiac events were shown among the 3 major LQTS genotypes (LQT1 versus LQT2: HR, 1.83; 95% CI, 0.36 to 9.17; \(P=0.46\); LQT3 versus LQT2: HR, 2.95; 95% CI, 0.26 to 33.16; \(P=0.38\); LQT3 versus LQT1: HR, 1.62; 95% CI, 0.18 to 14.47; \(P=0.67\)). Interactions among clinical factors and between clinical factors and genotypes were not significant in the model that included the genotyped population, possibly because of the relatively low event rate in this subset of study patients.

A QTc duration >500 ms was associated with a statistically nonsignificant 2-fold increase in the risk of ACA or SCD in the genotyped population (HR, 2.68; 95% CI, 0.69 to 10.49; \(P=0.16\)). Notably, no life-threatening cardiac events occurred in genotyped patients who exhibited low to normal QTc durations (<450 ms \([n=127]\)) whereas the cumulative probability of ACA or SCD in patients with intermediate (450 to 500 ms \([n=437]\)) and high (>500 ms \([n=239]\)) QTc durations was 1% and 3%, respectively (\(P=0.037\) for the comparison among the 3 QTc subgroups).

**β-Blocker Efficacy During Childhood**

β-Blocker therapy was initiated at some point during childhood for 643 study patients (21%), of whom 67 (10%) discontinued the medication before termination of follow-up. The main β-blocker subtypes and their respective mean dosages are shown in Table 2.

Patients who were treated with β-blockers during childhood had a higher frequency of risk factors compared with untreated LQTS children (QTc duration: 501±50 versus 489±48 ms, respectively \([P<0.001]\); prior syncope: 52% versus 12%, respectively \([P<0.001]\); male gender: 56% versus 33%, respectively \([P<0.001]\)).

In multivariable analysis, β-blocker therapy was independently associated with a significant 53% reduction in the risk of ACA or SCD during childhood (HR, 0.47; 95% CI, 0.26 to 0.85; \(P=0.01\)). The benefit of β-blocker therapy was pronounced among high-risk children who experienced syncope during the past 2 years (HR, 0.27; 95% CI, 0.12 to 0.62; \(P=0.002\)) and significantly attenuated (HR, 0.95; 95% CI, 0.41 to 2.21; \(P=0.90\)) in lower-risk children with more remote or no syncope (for β-blocker–by–recent syncope interaction, \(P=0.03\)). However, despite the significant beneficial effects of β-blockers, the rate of life-threatening cardiac events among high-risk children who were treated with β-blockers was considerable: Boys on β-blockers as of 6 years of age who experienced syncope before 6 years of age had a 12% cumulative probability of ACA or SCD during the subsequent 7 years of follow-up, corresponding to an average annual event rate of nearly 2% while on medical therapy.

**Other LQTS-Related Therapies During Childhood**

Additional therapeutic modalities were used infrequently during childhood and are considered separately below. Medical therapy with mexiletine and flecainide was administered to a small number of study patients (Table 2). Twenty-nine study patients received mexiletine, of whom 2 (7%) had ACA or SCD during treatment. Flecainide was administered to only 5 patients (mostly LQT3 genotype carriers or their family members), of whom 1 experienced SCD during therapy.

Forty-one study patients (1%) received an implantable cardioverter-defibrillator (ICD) during childhood. The device
was implanted at a mean ± SD age of 7.3 ± 0.5 years. Twelve patients experienced ACA before implantation, and 29 experienced at least 1 episode of syncope before implantation (mean ± SD, 2.5 ± 0.4 episodes). The combined end point of ACA or SCD occurred in 1 patient who was affected with Timothy syndrome (ICD implanted at 2.5 years of age as a result of recurrent syncope despite β-blocker therapy; age at death, 5.1 years; mode of death, electrical storm [persistent torsade de pointes despite 25 ICD shocks]) during a mean ± SD follow-up period of 2.7 ± 0.3 years. Interrogation data were available for a subset of 20 LQTS children (49%) with an ICD, of whom 8 (40%) experienced at least 1 appropriate ICD discharge during the same follow-up period.

Left cervical sympathetic denervation was carried out in 40 patients (1%) during childhood. The procedure was performed at a mean ± SD age of 7.4 ± 0.4 years. Similar to patients treated with an ICD, children who underwent left cervical sympathetic denervation experienced prior syncope (n = 27) or prior ACA (n = 13). None of the patients who underwent left cervical sympathetic denervation experienced a life-threatening cardiac event after the procedure during a mean ± SD follow-up period of 3.9 ± 0.4 years.

A cardiac pacemaker was implanted in 70 children at a mean ± SD age of 6.2 ± 0.4 years, 9 of whom had ACA before implantation. The combined end point of ACA or SCD occurred in 6 patients after implantation of a pacemaker during a mean ± SD follow-up period of 4.0 ± 0.5 years.

### Discussion

Three main implications emerge from the present study about the risk of life-threatening cardiac events in LQTS children: (1) risk factors for ACA or SCD can be assessed from clinical history and examination of the ECG and include male gender, a history of syncope at any time during childhood, and a QTc duration >500 ms; (2) significant interactions exist among the 3 clinical risk factors that can identify risk subsets in this population; and (3) β-blocker therapy is associated with a significant reduction in the risk of life-threatening cardiac events in LQTS children. However, the rate of ACA or SCD in high-risk children who experience syncope is still considerable despite β-blocker therapy.

The present study is the first to focus solely on the end point of life-threatening cardiac events in young, preadolescent LQTS children. We have shown that the rate of fatal or near-fatal events in children with this genetic disorder is significantly higher among boys than among girls throughout childhood, resulting in a significantly higher cumulative event rate in preadolescent boys despite the fact that girls exhibited a significantly longer mean QTc duration and had similar baseline heart rates. Notably, asymptomatic boys with a prolonged QTc duration exhibited a >12-fold increase in the risk of life-threatening cardiac events compared with the respective girls, whereas after the occurrence of syncope during follow-up, the relative risk associated with male gender was attenuated.

Our findings are consistent with previous data on gender differences in the risk of LQTS-related cardiac events. Two recent studies from the International LQTS Registry that have focused on LQTS adolescents and adults demonstrated that the gender-related risk reverses after childhood, and female patients maintain higher risk than male patients throughout adolescence and during adulthood. The mechanisms behind these age-dependent differences in gender-related risk are unknown. The predominance of life-threatening cardiac events among boys during the first decade of life may be related to environmental factors or to the presence of modifier genes, whereas the opposing effects of estrogen and androgens on ventricular repolarization (increase and decrease in QTc duration, respectively) have been suggested as a possible mechanism for the male versus female risk reversal with the onset of adolescence. Ventricular tachyarrhythmias have been shown to occur more frequently during physical effort in patients carrying the common LQT1 genotype, possibly because of a lack of adaptive QT shortening with decreasing RR intervals during tachycardia. Boys may participate more frequently in intensive physical activity than girls during childhood as a result of environmental influences, and this factor may contribute to the gender-related risk of life-threatening tachyarrhythmias in this age group. It also is possible that modifier genes exist that are not shared by boys and girls (eg, on the Y chromosome), which contribute to the higher risk of LQTS boys early in life. Thus, interactions among environmental, genetic, and hormonal factors need to be further evaluated in this genetic disorder. At present, our data suggest that LQTS boys should be followed up carefully for both QTc duration and the development of clinical symptoms and should be offered primary therapies for this genetic disorder during childhood on the basis of either of these 2 risk factors, whereas LQTS girls who do not experience syncope appear to maintain a relatively low risk for ACA or SCD during childhood regardless of their QTc duration.

Genotype data have been shown to be useful for risk stratification in LQTS patients when syncope is a component of the cardiac end point. However, in the present study, a history of syncope was used as a time-dependent covariate in the multivariable model that assessed the end point of ACA or SCD. Using this methodology, we have shown that among genotyped study patients, data on a specific genotype (LQT1, LQT2, or LQT3) did not contribute significantly to outcome, whereas clinical risk factors, including male gender and time-dependent syncope, maintained their significance as powerful predictors of outcome. Nevertheless, only 2% of genotyped patients experienced a fatal or near-fatal event during childhood. Thus, it is possible that the study may be underpowered to detect statistically significant differences in the risk conferred by the 3 main LQTS genotypes or interactions between clinical factors and genotypes. Similarly, despite the fact that children born with congenital deafness experienced a significantly higher frequency of life-threatening cardiac events (10%) compared with those without congenital deafness (2%), this factor did not make a significant contribution to outcome after multivariable adjustment, possibly because all patients with congenital deafness who had a life-threatening cardiac event during childhood also experienced syncope before the event, making the latter symptom the predominant risk factor in the multivariable model.
β-Blocker therapy was associated with a significant reduction in the risk of life-threatening cardiac events in the study population, with a more pronounced effect in high-risk patients who experienced recent syncope, suggesting that this mode of medical therapy should be considered a first-line measure in LQTS children. The lack of a significant effect of β-blocker therapy in lower-risk patients does not imply that this mode of medical therapy should not be prescribed to symptomatic boys or girls with remote syncope or boys with a prolonged QTc interval duration. β-Blockers were administered to those considered to be at risk by the treating physician, and unmeasured risk factors may have been more unbalanced in patients with lower-risk features. Nevertheless, despite the highly significant beneficial effects of β-blockers in high-risk children and the possible beneficial effects in lower-risk subsets, children with a history of syncope who were treated with β-blockers still displayed a substantial burden of life-threatening events while on medical therapy. Other therapeutic modalities, including implantation of an ICD and left cervical sympathetic denervation, have been shown to be effective in LQTS patients. These more invasive medical procedures should be considered for the primary prevention of life-threatening cardiac events in LQTS children in whom symptoms persist despite β-blocker therapy.

Study Limitations

Despite the relatively large sample size of the present study, only 53 first life-threatening cardiac events were recorded in boys and, more importantly, only 20 among girls. This relatively low event rate, especially among girls, could have contributed to the unexpectedly large 12- to 28-fold HR estimates for remote and recent syncope among girls and the 4.5-fold interaction of gender with syncope. Therefore, although these effects were statistically significant at the 0.01 level, future analyses of the expanding LQTS Registry may be needed to validate and better estimate the identified interactions with gender, the relative risks among girls and the effect of genetic factors on outcome during childhood.

Conclusions and Clinical Implications

The present study of LQTS children and a recent report from the International LQTS Registry on the clinical course of LQTS adolescents consistently demonstrate that risk factors for life-threatening cardiac events can be assessed from clinical history and the surface ECG. Importantly, the results of the 2 studies suggest that careful follow-up is warranted in LQTS patients because risk factors for life-threatening cardiac events are time dependent and age specific, resulting in a substantial variability in the phenotypic expression of this genetic disorder during long-term follow-up.

Sources of Funding

This work was supported by research grants HL-33843 and HL-51618 from the National Institutes of Health, Bethesda, Md, and by a research grant to the University of Rochester from Genaissance Pharmaceuticals.

Disclosures

The University of Rochester (Dr Moss) received a grant from Genaissance Pharmaceuticals that supported research for the detection of LQTS-related ion channel mutations. Dr Ackerman reports that he is a consultant for Clinical Data (formerly Genaissance Pharmaceuticals) with respect to the FAMILION genetic test for cardiac ion channel mutations and holds significant interest in intellectual property related to ion channel patents. The other authors report no conflicts.

References


CLINICAL PERSPECTIVE

The congenital long-QT syndrome (LQTS) is an important cause of sudden cardiac death in young individuals without structural heart disease. However, data on risk factors for life-threatening cardiac events in children with this genetic disorder are limited. The present study assessed the risk of aborted cardiac arrest or sudden cardiac death in a population of 3015 LQTS children 1 through 12 years of age who were enrolled in the International LQTS Registry. Using time-dependent multivariable analysis, we identified male gender, QTc duration, and a history of prior syncope as risk factors for life-threatening cardiac events in LQTS children. Furthermore, we demonstrate that significant interactions exist among these 3 clinical risk factors that may be used to identify risk subsets in this population. Notably, β-blocker therapy is shown to be associated with a significant reduction in the risk of life-threatening cardiac events during childhood, with a more pronounced benefit (73% risk reduction) in high-risk children who experience recent syncope. However, the rate of life-threatening cardiac events in high-risk children who are treated with this mode of medical therapy is still considerable, with an average annual event rate of 2% while on medical therapy. These findings suggest that careful follow-up is warranted in LQTS children because risk factors for life-threatening cardiac events in this population are time dependent and age specific, resulting in a substantial variability in the phenotypic expression of LQTS during long-term follow-up.
Risk Factors for Aborted Cardiac Arrest and Sudden Cardiac Death in Children With the Congenital Long-QT Syndrome


_Circulation_. 2008;117:2184-2191; originally published online April 21, 2008;
doi: 10.1161/CIRCULATIONAHA.107.701243

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/117/17/2184

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2008/04/28/CIRCULATIONAHA.107.701243.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/