LONG QT SYNDROME (LQTS) IS A genetic disease characterized by prolonged ventricular repolarization, syncope, ventricular arrhythmias, and sudden death,1,3 often precipitated by emotion or exercise. Primarily according to nonrandomized trial evidence, β-blockers are considered first-line prophylactic therapy,4 whereas pa-
tients refractory to therapy may be treated with left-sided cardiac sympathetic denervation, pacemakers, or implantable cardioverter defibrillators.1,3-8 The hypothesis that the efficacy of therapy may vary according to the genetic form of the disease has been proposed7 but not thoroughly investigated.

Three genetic loci account for nearly 98% of genetically characterized patients. In this investigation, we sought to describe and assess outcomes of β-blocker–treated patients affected by the 3 most common genetic loci of LQTS: LQT1, LQT2, and LQT3, caused by genetic defects on KCNQ1, KCNH2, and SCN5A genes.

## METHODS

### Study Population and Data Collection
The study population included 335 genotyped LQT1, LQT2, or LQT3 patients treated with long-term β-blocker therapy. For each patient, data on personal and family history, cardiac events, and therapy were systematically re-
corded at each visit or medical contact. The specific β-blocker used, as well as dose, was at the discretion of the treating physician. LQTS-related cardiac events included unexplained syncope, torsades de points, ventricular tachycardia, aborted cardiac arrest, and sudden cardiac death. All patients or their guardians provided written in-
fom consent for clinical and ge-
netic studies.

### Design, Setting, and Patients
Consecutive LQTS-genotyped patients (n=335) in Italy treated with β-blockers for an average of 5 years.

### Main Outcome Measures
Cardiac events (syncope, ventricular tachycardia/torsades de points, cardiac arrest, and sudden cardiac death) while patients received β-blocker therapy according to genotype.

#### Results
Cardiac events among patients receiving β-blocker therapy occurred in 19 of 187 (10%) LQT1 patients, 27 of 120 (23%) LQT2 patients, and 9 of 28 (32%) LQT3 patients (P<.001). The risk of cardiac events was higher among LQT2 (adjusted relative risk, 0.81; 95% confidence interval [CI], 1.50-5.27; P=.001) and LQT3 (adjusted relative risk, 4.00; 95% CI, 2.45-8.03; P<.001) patients than among LQT1 patients, suggesting inadequate protection from β-blocker therapy. Other important predictors of risk were a QT interval corrected for heart rate that was more than 500 ms in patients receiving therapy (adjusted relative risk, 2.01; 95% CI, 1.16-3.51; P=.01) and occurrence of a first cardiac event before the age of 7 years (adjusted RR, 4.34; 95% CI, 2.35-8.03; P<.001).

#### Conclusion
Among patients with genetic LQTS treated with β-blockers, there is a high rate of cardiac events, particularly among patients with LQT2 and LQT3 genotypes.

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genetic evaluation. The protocol was approved by the institutional review board of the Policlinico S. Matteo and of the Maugeri Foundation, Pavia, Italy.

**Genetic Analysis**

Patients were consecutively genotyped at the Molecular Cardiology Laboratories of the Maugeri Foundation as carriers of a single mutation on KCNQ1, KCNH2, or SCN5A genes; carriers of double mutations, representing on average 3% to 5% of the patients, were excluded from the study.

DNA was extracted from peripheral blood lymphocytes and amplified with primer pairs for KCNQ1, KCNH2, and SCN5A. Genetic analysis was performed by standard methods: denaturing high-performance liquid chromatography (Wave Transgenomics, Omaha, Neb) was performed on polymerase chain reaction–amplified DNA, encompassing the entire open reading frame of each gene, by using intronic primers. When abnormal chromatograms were identified, double-strand sequencing of amplified genomic DNA (ABI Prism 310; Applied Biosystems, Foster City, Calif) of the corresponding amplicon was performed. In addition to the previously reported polymorphisms, all DNA variants causing coding variations and occurring in more than 1 in 100 of the control population (400 healthy controls; ie, 800 alleles) were considered polymorphisms.

**Statistical Analysis**

All analyses were performed with the SPSS 11.0 statistical package (SPSS Inc, Chicago, Ill). Statistical significance was set at \( P \leq .05 \). Genetic loci–related differences for continuous variables were assessed by using 1-way analysis of variance, with post hoc analysis with the Tukey test, whereas differences for categorical variables were assessed with the Pearson \( \chi^2 \) test. Survival analyses included construction of Kaplan-Meier plots with comparisons with the log-rank \( \chi^2 \) test, as well as forward-selection Cox proportional hazards modeling. We considered sex, QT interval corrected for heart rate (QTc), occurrence of cardiac events before therapy, age at first cardiac event before therapy, family history of sudden death, and genotype as candidate variables.

**RESULTS**

**Population Characteristics**

The 335 genotyped LQTS patients were from 187 families with mutations on KCNQ1 (LQT1; \( n = 187 \)), KCNH2 (LQT2; \( n = 120 \)), or SCN5A (LQT3; \( n = 28 \)) genes treated with \( \beta \)-blockers. Before therapy, 159 of 335 (47%) experienced cardiac events. The mean (SD) age at initiation of \( \beta \)-blocker therapy was 21 (17) years (interquartile range, 8.5-31.7 years); the median follow-up for patients without events and receiving \( \beta \)-blocker therapy was 4.7 years (range, 0.6-36 years). As summarized in TABLE 1, no differences among LQT1, LQT2, and LQT3 patients were observed in age, age at initiation of therapy, observation time while receiving \( \beta \)-blockers, and age at first cardiac event before therapy. However, LQT1 patients had a shorter QTc interval. Data for type of \( \beta \)-blocker and dosage per kilogram of body weight were available for 266 individuals: 69% of them were treated with either propranolol (average daily dose, 2.2 [SD, 1.04] mg/kg) or nadolol (average daily dose, 1.2 [SD, 0.5] mg/kg); there were no dosage differences among the 3 genotypes (\( P = .31 \)).

**Cardiac Events in Patients Receiving \( \beta \)-Blocker Therapy**

There were 55 patients (16%) who experienced cardiac events while receiving \( \beta \)-blocker therapy, of whom 14 (25%) had a cardiac arrest; 4 sudden cardiac deaths occurred (1 LQT1 and 3 LQT3). Events were not evenly distributed in the 3 loci, with LQT1 having the lowest incidence of cardiac events (LQT1: 19/187 [10%]; LQT2: 27/
in patients receiving therapy include QTc interval and younger age at a first pretherapy cardiac event.

Because no randomized trial data exist, our findings about the value of defibrillator therapy could be safely discontinued after defibrillator implantation.

**Table 2.** Significant Predictors of Cardiac Events and Cardiac Arrest for Patients Receiving Therapy (N = 335)

<table>
<thead>
<tr>
<th>Predictors of Cardiac Events</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First cardiac event before therapy in early childhood (≤7 y)</td>
<td>4.34 (2.35-8.03)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>QTc &gt;500 ms while receiving therapy</td>
<td>2.01 (1.16-3.51)</td>
<td>.01</td>
</tr>
<tr>
<td>Genetic locus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LQT2 vs LQT1</td>
<td>2.81 (1.50-5.27)</td>
<td>.001</td>
</tr>
<tr>
<td>LQT3 vs LQT1</td>
<td>4.00 (2.45-6.38)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; QTc, QT interval corrected for heart rate with Bazett formula.
This study is based on an observational registry and is subject to all the inherent limitations of such an analysis. Because LQTS is a relatively rare disease, it is unlikely that large-scale randomized trial data will become available soon, meaning that evaluation and treatment of these patients must occur in a setting of incomplete evidence. Furthermore, approximately 40% of LQTS patients cannot be genotyped on the known loci, so for these patients, β-blockers remain the recommended therapy.

**Author Contributions:** Drs Priori, Grillo, Bloise, Napolitano, and Schwartz had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Study concept and design:** Priori, Napolitano, Schwartz.

**Acquisition of data:** Napolitano, Grillo, Bloise, Ronchetti, Moncalvo, Veia, Bottelli, Nastoli.

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**Obtained funding:** Priori, Schwartz.

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**Study supervision:** Priori, Napolitano, Schwartz.

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**REFERENCES**


Words ought to be a little wild for they are the assaults of thought on the unthinking.

—John Maynard Keynes (1883-1946)