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Interplay Between Genetic Substrate, QTc Duration, and Arrhythmia Risk in Patients With Long QT Syndrome

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ABSTRACT

BACKGROUND Long QT syndrome (LQTS) is a common inheritable arrhythmogenic disorder, often secondary to mutations in the *KCNQ1*, *KCNH2*, and *SCN5A* genes. The disease is characterized by a prolonged ventricular repolarization (QTc interval) that confers susceptibility to life-threatening arrhythmic events (LAEs).

OBJECTIVES This study sought to create an evidence-based risk stratification scheme to personalize the quantification of the arrhythmic risk in patients with LQTS.

METHODS Data from 1,710 patients with LQTS followed up for a median of 7.1 years (interquartile range [IQR]: 2.7 to 13.4 years) were analyzed to estimate the 5-year risk of LAEs based on QTc duration and genotype and to assess the antiarrhythmic efficacy of beta-blockers.

RESULTS The relationship between QTc duration and risk of events was investigated by comparison of linear and cubic spline models, and the linear model provided the best fit. The 5-year risk of LAEs while patients were off therapy was then calculated in a multivariable Cox model with QTc and genotype considered as independent factors. The estimated risk of LAEs increased by 15% for every 10-ms increment of QTc duration for all genotypes. Intergenotype comparison showed that the risk for patients with LQT2 and LQT3 increased by 130% and 157% at any QTc duration versus patients with LQT1. Analysis of response to beta-blockers showed that only nadolol reduced the arrhythmic risk in all genotypes significantly compared with no therapy (hazard ratio: 0.38; 95% confidence interval: 0.15 to 0.93; $p = 0.03$).

CONCLUSIONS The study provides an estimator of risk of LAEs in LQTS that allows a granular estimate of 5-year arrhythmic risk and demonstrate the superiority of nadolol in reducing the risk of LAEs in LQTS. (J Am Coll Cardiol 2018;71:1663–71) © 2018 by the American College of Cardiology Foundation.

The genetic background of long QT syndrome (LQTS), an inherited disease that predisposes young patients to sudden cardiac death (1), was largely discovered between 1995 and 1996 when Mark Keating's laboratory identified the first 3 genes associated with the disease: *KCNQ1* (LQT1) (2), *KCNH2* (LQT2) (3), and *SCN5A* (LQT3) (4).

In the first 10 years after the discovery of these major LQTS genes (1995 to 2006), efforts were dedicated to identifying novel mutations and

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

HR = hazard ratio

LAE = life-threatening arrhythmic event

LQTS = long QT syndrome

QTc = corrected QT interval

RCS = restricted cubic spline

characterizing their functional effect. These studies paved the way for the development of the contemporary risk stratification strategy in LQTS, which is based on the early evidence that arrhythmic risk is modulated by the duration of corrected QT (QTc) interval and the genetic substrate (5,6).

In the following decade (2007 to 2017), next-generation sequencing allowed for the identification of novel genes and established genetic testing as a pivotal element in the clinical management of patients. As of today, 17 genes have been associated with LQTS, although the majority of patients carry mutations in 3 genes: *KCNQ1*, *KCNH2,* or *SCN5A* (7). Despite the innovation introduced by genetic screening, the management of patients has advanced slowly, and the target of a personalized approach to treatment has not yet achieved a level of evidence sufficient for its incorporation in the guidelines for critical practice.

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In the present study, we analyzed data from our cohort of 1,710 patients with LQTS to characterize the diversity of clinical manifestations of the disease, propose a granular model for the assessment of arrhythmic risk, and compare the effect of different beta-blockers in reducing the occurrence of life-threatening arrhythmias. This latter point has a high clinical relevance, because even though nadolol is the treatment recommended by several tertiary referral centers (8), no evidence-based data exist on whether it is superior to other beta-blockers in reducing the occurrence of sudden cardiac death and cardiac arrest.

METHODS

STUDY POPULATION. The study was conducted on 1,710 individuals from 812 families followed up at our clinics and genotyped as carriers of a single mutation in one of the major LQTS genes: *KCNQ1*, *KCNH2*, or *SCN5A*. Patients who were carriers of double mutations (e.g., those with Jervell and Lange-Nielsen syndrome) and those who carried genetic variants adjudicated as benign or likely benign according to the criteria proposed by the American College of Medical Genetics and Genomics (9) were excluded from the current study. Clinical data were filed in a custom-made registry and included demographic information, personal and family history of symptoms, arrhythmic events, electrocardiographic parameters, and therapies at enrollment and during follow-up.

For the measurement of electrocardiographic parameters, we adopted the methodology introduced by the Long QT Syndrome International Registry (10) that is now largely adopted in the field (11). Accordingly, we obtained the first available 12-lead electrocardiogram (paper speed 25 mm/s and voltage settings 10 mm/mV) before therapy when accessible, at stable heart rates close to 60 beats/min during daylight hours to limit the confounding effect of diurnal variability of QT interval (12). The QT interval duration was measured in lead DII or V5 and corrected for the heart rate using the Bazett formula.

The study protocol was approved by the ethics committee of the IRCCS (Institute for Research and Health Care), ICS (Clinical Science Institute) Maugeri, Pavia, Italy. All patients or their guardians provided written consent to grant access to their clinical data for investigational purposes.

GENETIC ANALYSIS. Genetic analysis was performed at our institution, either by Sanger sequencing (ABI PRISM 330, Thermo Fisher, Waltham, Massachusetts) or next-generation sequencing (Ion Torrent Personal Genome Machine, Thermo Fisher, Waltham, Massachusetts) on the 3 key genes associated with LQTS, in accordance with the current recommendations (13). The genetic variants included in the study were evaluated independently by 2 groups (Molecular Cardiology Laboratory at ICS Maugeri and Health in Code, La Coruña, Spain) according to the criteria proposed by the American College of Medical Genetics and Genomics (9). Eighty-nine percent of patients included in the study had a pathogenic or likely pathogenic mutation, and 11% of patients had a variant of uncertain significance.

STATISTICAL ANALYSIS. Statistical analysis (V.B., E.P.) was performed with SAS version 9.4 (SAS Institute, Cary, North Carolina). Data are expressed as percentage or mean ± SD. Continuous variables were compared with unpaired Student's *t*-test, and categorical variables were compared with the chi-square test.

The cumulative incidence of a first life-threatening arrhythmic event (LAE) (sudden cardiac death, aborted cardiac arrest, and hemodynamically non-tolerated polymorphic ventricular tachycardia) during follow-up was defined from the date of LQTS diagnosis to the first LAE. Deaths attributable to nonarrhythmic causes were considered competing events. In instances with no events, the observation was censored at the last visit. The Gray test was used to assess the difference in the cumulative incidence of the first LAE between subgroups of patients (14). Multivariable Cox proportional hazards models were used to evaluate the effects of sex, genotype, QTc duration, history of LAEs before diagnosis of LQTS, occurrence of syncope, and beta-blocker therapy on the risk of experiencing an LAE.