Risk Stratification in the Long QT Syndrome

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KEYWORDS

• Long QT syndrome • Sudden death • Risk stratification

Concrete advances have been taken in the past 55 years in the comprehension and management of inherited pathologies that predispose individuals to an increased risk of sudden cardiac death (SCD). Since the first observation by Jervell and Lange-Nielsen[1] of "four cases of deaf-mutism combined with a marked prolongation of the QT interval and a serious outcome," physicians and scientists worldwide have collaborated to make the long QT syndrome (LQTS) the most investigated inherited arrhythmogenic syndrome. Several registries that have collected thousands of patients have allowed the natural history of this syndrome to be defined,[2,3] which has an estimated prevalence of 1 in every 2000 live births.[4]

ß-Blockers (especially in the context of specific LQTS subtypes; **Fig. 1**) have shown their efficacy in protecting most patients from dangerous ventricular arrhythmias and have dramatically improved the natural history of the disease.[5,6] A minority of affected individuals, however, remain at risk despite antiadrenergic therapy,[6] and therefore it has become of paramount importance to identify these patients and direct them to alternative and more aggressive therapeutic strategies, including cardiac denervation and an implantable cardioverter-defibrillator (ICD). An appropriate risk stratification scheme is pivotal to preventing sudden death while avoiding overtreatment.

Risk stratification is an evolving concept that began from the observation of clinical parameters (history of symptoms, QT duration, age, gender) and subsequently integrated knowledge from molecular studies (gene-specific initially, and mutation-specific in a future perspective).[3] Currently, the concept of determining individual risk is based on a well-established framework of clinical and genetic characteristics. A history of aborted cardiac arrest or syncope is the best predictor for future events. In asymptomatic individuals, corrected QT duration (QTc, $\geq$500 ms) is a good indicator for risk stratification, especially when combined with demographic and genetic characteristics (age, gender, LQTS subtype).

This article presents detailed data regarding the risk predictors in LQTS.

CLINICAL RISK PARAMETERS

Symptoms

LQTS exposes patients to an increased risk of fatal (SCD) and nonfatal arrhythmic events that persist from an early age and progress almost unabated until adulthood.[3] The overall annual rate of SCD in patients with untreated LQTS is approximately 0.9%.[7]

Syncope is a frequent event in patients with LQTS, with an annual rate of approximately 5%

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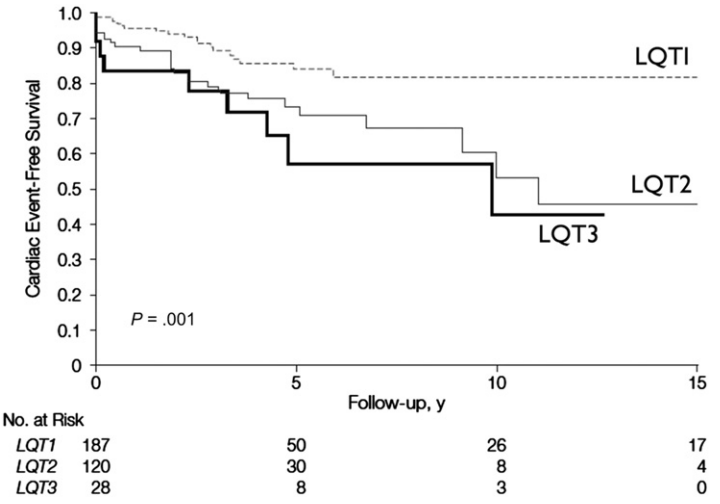

Fig. 1. Kaplan-Meier analysis of cumulative cardiac event-free survival in patients with genotyped LQTS receiving ß-blockers according to the genetic variant of the disease (P = .001 by the log-rank test). The definition of events included syncope, cardiac arrest, and sudden cardiac death. LQT1, long QT syndrome type 1; LQT2, long QT syndrome type 2; LQT3, long QT syndrome type 3. (*From* Priori SG, Napolitano C, Schwartz PJ, et al. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. JAMA 2004;292:1343; with permission.)

in untreated patients, and some variability based on the underlying genetic defect.[3] Although probably not all syncopes observed in patients with LQTS are caused by arrhythmic events, a clinical history of a syncopal event is a strong predictor of adverse outcome.[7,8] A single syncopal event has been associated with a sixfold increase in the risk of subsequent SCD.[9] Jons and colleagues[10] showed that patients who experience multiple syncopes in the absence of ß-blocker treatment have twice the risk of experiencing a cardiac event compared with patients who have a single syncopal event (hazard ratio [HR], 1.8; P<.001). Additionally, this study showed that the occurrence of syncope during ß-blocker treatment is the most powerful predictor of subsequent life-threatening events (HR, 3.6; P<.001; **Fig. 2**) and indicates the need for more aggressive therapies. The risk of ß-blocker failure is apparently highest in young children and women.[10]

QT Interval Duration

Recording of 12-lead surface electrocardiogram and accurate measurement of QT interval corrected for heart rate (QTc) represent the basic evaluation for establishing the diagnosis of LQTS. As with most biologic parameters, the QT interval varies in relation to age and sex,[11] and is also modulated by fluctuations in heart rate or the autonomic tone. Besides being the hallmark of the syndrome, a prolonged QTc interval represents an effective indicator of risk in patients with LQTS.

That the probability of SCD and ventricular arrhythmias is strictly related to the magnitude of prolongation of the QT interval was originally shown in a study of the International Long QT Syndrome Registry in 1991.[7]

With the progressive importance that genetics has gained in the field, it seemed reasonable to reassess whether the introduction of genotype to the

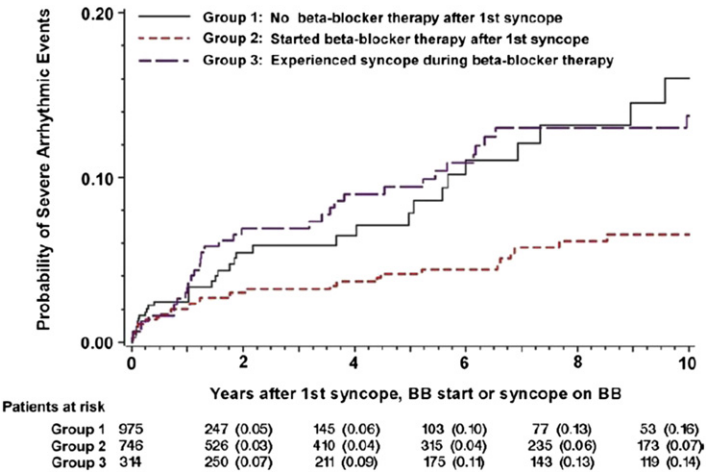

Fig. 2. The cumulative risk of severe arrhythmic events and ß-blocker (BB) therapy. The solid black line represents all patients after the first syncopal event until the start of BB therapy, and the red dashed line represents patients after the start of therapy. Patients with a syncopal event occurring while off BB therapy are represented by the purple dashed line. (*From* Jons C, Moss AJ, Goldenberg I, et al. Risk of fatal arrhythmic events in long QT syndrome patients after syncope. J Am Coll Cardiol 2010;55(8):785; with permission.)