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Editorial Commentary: Triggers for cardiac events in patients with type 2 long QT syndrome

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The congenital long QT syndromes (LQTS) are a group of genetic disorders that affect cardiac ion channels, are characterized by prolongation of the QT interval, and carry a high risk for the life-threatening polymorphic ventricular tachycardia, Torsades de Pointes. Shortly after the autosomal recessive syndrome of congenital deafness, prolongation of the QT interval, and sudden cardiac death was described by Anton Jervell and Fred Lange-Nielsen in 1957,¹ Romano and Ward each independently described an “autosomal dominant” form without congenital deafness.^{2, 3} However, it was not until the late 1990’s that the first 5 LQTS genes were identified, all of which encode ion channel subunits that underlie the cardiac action potential.^{4–7} The most commonly affected genes, *KCNQ1* and *KCNH2* (underlying LQT1 and LQT2 respectively), encode proteins that form the α -subunits of 2 major repolarizing potassium currents, *IKs* and *IKr*. Two other LQTS genes encode for the corresponding β -subunits (*KCNE1* and *KCNE2* underlying LQT5 and LQT6, respectively). The other major LQTS gene, *SCN5A* (underlying LQT3) encodes the α -subunit of the cardiac sodium channel. Additional ion channel mutations have been associated with rare arrhythmia syndromes (Andersen-Tawil syndrome [ATS], *KCNJ2* and Timothy syndrome, *CACNA1C*) which may include QT prolongation, as well as significant extracardiac phenotypes.⁸ ATS patients do not uniformly display prolonged QT intervals, and due to clinical features that differ from LQTS, is better termed ATS1 rather than LQT7.⁹ The previously-termed LQT4 has been linked to mutations in *ANK2*, encoding the structural protein ankyrin-B, which when mutated, results in altered localization and expression of ion channels.¹⁰

The estimated prevalence of congenital LQTS is in the range of 1 in 5,000 individuals. However, the true prevalence of the overt or subclinical disorder is likely to be considerably higher as approximately 10% of patients harbor 2 LQTS mutations. Approximately 13% of LQTS patients will suffer cardiac arrest or sudden cardiac death before the age of 40 years without therapy; when syncopal events are included, 36% will have symptoms by age 40.¹¹ The Jervell-Lange-Nielsen syndrome is more severe, with 90% experiencing syncope, cardiac arrest, or sudden death by age 18, and mortality exceeds 25% even with therapy.¹² Important clinical differences among affected patients depending on the underlying affected gene have been observed so called genotype-phenotype correlation. As the majority (>90%) of genotyped LQTS patients have LQT1, LQT2, or LQT3 most of the differences are observed among these genotypes, and include different ECG T-wave patterns,¹³ clinical course,¹⁴ triggers of cardiac events,¹⁵ response to sympathetic stimulation,^{16, 17} and effectiveness and limitations of β -blocker therapy.¹⁸

Life-threatening cardiac events such as syncope or sudden death tend to occur under specific circumstances in a gene-specific manner. In patients with the LQT1 genotype, cardiac events are often triggered by vigorous physical activity. In contrast, LQT2 patients are at high risk for arrhythmic events with sudden loud noise, such as ringing of an alarm clock or telephone. Even more distinct in terms of triggering events are LQT3 patients, who experience their cardiac events without emotional arousal during sleep or at rest. The triggering role of sympathetic activation in LQT1 and LQT2 has important therapeutic implications, and as discussed below, it suggests that protection could be expected by the use of anti-adrenergic therapy.

Previous LQTS studies have focused on the identification of genotype-specific risk factors for cardiac events. In this issue of *Heart Rhythm*, Kim et al.¹⁹ took a different approach and asked the question whether clinical and genetic risk factors exhibit a trigger-specific association with cardiac events in patients with LQT2. The study population comprised of 634 genetically-confirmed LQT2 patients from the US portion of the International LQTS Registry. This Registry, established in 1979, has provided important insights into many aspects of congenital LQTS including risk mechanisms, genotype-phenotype relations, risk stratification by clinical characteristics and molecular subtypes and the importance of syncope as a predictor of aborted cardiac arrest or sudden cardiac death.

In this study, trigger-specific events were categorized as arousal, exercise-induced and non-arousal/non-exercise induced. In 44% of patients with LQT2 genotype, the first cardiac event was triggered by sudden arousal. A much smaller percentage (13%) was associated with exercise and in the remainder of the patients (43%), cardiac events were associated with a highly heterogeneous group of triggers that were unrelated to sudden arousal or exercise. Each of the 3 trigger-specific events were associated with individual risk factors which included sex, location and type of mutation, and QTc prolongation. The most surprising result of the study was the differential effect of β -blockers on reducing the risk of cardiac events. Only in exercise-triggered events did β -blockers decrease the risk of cardiac events; there was a non-significant effect on risk of arousal and non-exercise/non-exercise triggered cardiac events.

The authors make a strong argument for a trigger-specific approach in the risk assessment and management of LQT2 patients. However, before implementing such an approach, a number of issues might warrant further consideration. First, basing the initial therapy for LQT2 patients purely on age, sex and location of the mutation might be problematic as there is a greater than 50% chance that the first cardiac event may not be arousal-triggered. Furthermore, 13% and 17% of patients who experienced a first arousal and non-exercise/non-arousal triggered event, respectively, experienced a subsequent triggered event that was not of the same type. Thereby, as the authors point out, β -blockers should not only be administered to patients who experience an exercise triggered event but also those who experience their first non-exercise triggered cardiac event. I agree that once a patient has declared themselves with a non-exercise triggered event, then more aggressive treatment may be warranted in this sub-group. Second, the differential response to beta-blockers is surprising and unexpected. Many physician-investigators currently advocate administering β -blockers to all LQTS patients, even those at low risk. Earlier studies have clearly shown that suppression of adrenergic-mediated triggers with β -blockers in patients with LQT1 and LQT2 was associated with a significant reduction in the rate of cardiac events but this reduction was not evident in those with LQT3 mutations.¹⁸ Although data regarding therapies was obtained through pre-specified questionnaires from patients, family members, or referring physicians, it still remains subjective and possibly inaccurate especially when it comes to compliance with β -blockers in teenagers and young adults. These medications are

poorly tolerated by this group and often compliance is a significant problem and this may have biased the results.

In conclusion, Kim et al.¹⁹ have identified trigger-specific risk factors in patients with LQT2 genotype. This may not only aid in the risk stratification of individuals with this genotype but this data may also be used to guide therapy. Patients with LQT2 may now be individually managed based on trigger-specific risk factors, mutation location, type and topology as well as traditional risk factors such as QTc, sex or a history of prior syncope.

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