

Do patients with long QT syndrome remain at risk for sudden cardiac death after 40 years of age?

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SUMMARY

Long QT syndrome (LQTS) is an inherited arrhythmic disorder in which patients display a propensity for prolongation of the heart rate-corrected QT interval (QTc) and for sudden cardiac death. To obtain a better understanding of this disease, the International LQTS Registry was initiated in 1979, and has been an invaluable source of data on patients aged 40 years and younger with LQTS. The registry collaborators have now described 2,759 LQTS patients and controls aged older than 40 years. In this age group, a prolonged QTc, syncope in the last 10 years, and LQTS-3 were found to be the most important predictors of death from any cause or cardiac arrest requiring defibrillation in patients with LQTS (hazard ratios 2.65–9.92). Clearly, patients with LQTS remain at increased risk of lethal events after 40 years of age, indicating that continuous, age-independent awareness for QT prolongation is essential.

KEYWORDS arrhythmia, long QT syndrome, sudden cardiac death

COMMENTARY

With every heart beat, ion channels conduct sodium, potassium, and calcium ions across the membrane of cardiac myocytes. Congenital long QT syndrome (LQTS) is caused by mutations in genes encoding cardiac ion channel proteins, resulting in prolongation of the heart rate-corrected QT interval (QTc).¹ Moreover, polymorphic ventricular arrhythmias in patients with this disease lead to an increased risk of sudden cardiac death (SCD) at young age. Most patients with LQTS have a mutation in one of the cardiac ion channel encoding genes *KCNQ1*, *KCNH2*, or *SCN5a*, which results in LQTS-1, LQTS-2, or LQTS-3 respectively.¹ The incidence of LQTS-causing mutations is estimated at 1 in 2,000, but fortunately the majority of mutation carriers never experience LQTS-related symptoms.¹

To obtain a better understanding of the natural history of LQTS, its clinical features, and the long-term efficacy of different therapeutic approaches, a world-wide prospective study was initiated in 1979 by the International LQTS Registry Investigators.² As a result of the continuing efforts of the collaborators, this registry is now the largest case–control study of patients with LQTS and their unaffected family members in the world. The registry has been an invaluable source of information on the

gene-specific risk factors, treatment outcomes, and survival of patients with LQTS aged 40 years or younger but, until now, data on older patients were not reported. Consequently, it was not well known whether the increased risk of SCD in patients with LQTS extends beyond 40 years of age and whether this risk is affected by QTc, age, sex, or genotype. In a report published in *Circulation*, the registry collaborators have now addressed these issues for the first time.³

The study population in this analysis comprised 2,759 patients (58% female) aged between 41 years and 75 years (mean age 45.3 ± 14.5 years at enrollment) who underwent 19.0 ± 13.5 years of follow-up. Female patients with LQTS who had a prolonged QTc were found to have a higher cumulative probability of events (death from any cause or cardiac arrest requiring defibrillation) than females with a borderline or normal QTc. In men, however, QTc was not a predictor of events because males with a normal or borderline QTc had more events than their female counterparts. The risk of events was equally high among males and females with a prolonged QTc. In multivariate analyses, the hazard ratio (HR) for events among LQTS patients aged between 41 years and 60 years with a prolonged QTc was 2.65. In this age group, patients with LQTS-3 seemed to be at higher risk than genotype-negative patients (HR 4.76), in contrast to patients with LQTS-1

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or LQTS-2 (HRs 1.01 and 2.66, respectively, both nonsignificant). Moreover, among patients with LQTS who had a prolonged QTc, those with a history of syncope in the past 10 years had HRs between 2.76 and 9.92.

Therapy with β -blockers was most common among LQTS patients with a prolonged QTc (53%). In patients who had experienced syncope in the past 10 years, β -blocker therapy was associated with a nonsignificant, 42% reduction in the risk of events in individuals aged 41–60 years, and a marginally significant, 86% reduction in the risk of events in those aged 61–75 years. An implantable cardioverter-defibrillator was used in 6% of patients, but a detailed analysis of these individuals was precluded by a relatively short follow-up of 3.5 years.

This study clearly adds considerably to our knowledge of LQTS. The International LQTS Registry now covers in detail the real-life experiences of patients with LQTS aged 1–75 years. The results of the current study were not, however, unexpected. Earlier work showed that, in general, the risk of events in patients with LQTS-1 is particularly high from birth until around 20–30 years of age.^{4–6} The risk in patients with LQTS-2 starts just before or around adolescence and levels-off around the age of 30–40 years (but plateaus less than in patients with LQTS-1). The risk of events in patients with LQTS-3 also begins to increase in adolescence, but keeps rising indefinitely. Moreover, the acknowledged risk factors for events in patients with LQTS—prolonged QTc and syncope—remain important risk factors throughout life. Sex-related differences in LQTS are complex and are also influenced by interactions between patient age, QTc, and genotype. Under the age of 30–40 years, males with a prolonged QTc, particularly those with LQTS-3, seem to be at highest risk.⁵ Although there is variation between genotypes, female risk starts to increase around adolescence and at 30–40 years of age eventually levels with male risk. It is now clear that, after 40 years of age, the risk of events in male and female LQTS patients with a prolonged QTc is equal.³ An increase in the incidence of cardiovascular disease with rising age would be expected to result in more events in LQTS patients with a propensity for arrhythmias. Indeed, in the

analysis by the International LQTS Registry Investigators, the number of cardiac arrests was higher in patients with a prolonged QTc.³ This finding highlights the importance of adequate therapy. Treatment with β -blockers should be the rule rather than the exception in LQTS patients with syncope in the last 10 years or prolonged QTc. If severe symptoms remain despite the maximum dose of β -blockers, insertion of an implantable cardioverter-defibrillator should be considered. Furthermore, QTc-prolonging drugs⁷ and hypokalaemia should be avoided in all patients with LQTS.

Notwithstanding the limitations of registries, including a bias towards the enrollment of more severe cases and the observational design, the International LQTS Registry now gives us a comprehensive view of LQTS in all age groups. This study emphasizes that recognition of LQTS, accurate assessment of the QTc,⁸ and continuing detailed assessment of symptoms are critical to prevent SCD in older patients, as well as in those younger than 40 years of age.

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CLINICAL ADVANCE

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Competing interests

The authors declared no competing interests.