

Saving Lives in Congenital Long QT Syndrome: Who Benefits from Implantable Cardioverter Defibrillator Therapy?

ELIZABETH S. KAUFMAN, M.D.

From the Heart & Vascular Research Center, MetroHealth Campus of Case Western Reserve University, Cleveland, Ohio, USA

Editorial Comment

In the past decade, there has been an explosion in our understanding of the genetic and molecular basis of the congenital long QT syndromes (LQTS). LQTS is a group of genetically transmitted ion channel diseases in which patients demonstrate abnormal myocardial repolarization and may present with syncope or sudden death.^{1,2} Prolongation of cellular repolarization can result from one of several mutations causing loss of function of outward potassium currents or gain of function of inward sodium current.^{3,4} Clinical manifestations and severity of LQTS can depend upon the gene involved⁵ and the location of the mutation within the gene.⁶

Despite these advances in our understanding of the genetic basis for LQTS, our understanding of the best treatment for individual patients with LQTS remains incomplete. Since the 1970s, antiadrenergic therapy with beta-blockers and with left cardiac sympathetic denervation has been the mainstay of treatment for LQTS, as documented in reports of the International Long QT Registry.⁷ In 1985, Schwartz and Locati⁸ reported a study that demonstrated the dramatic efficacy of antiadrenergic therapy: the >53% 15-year mortality of LQTS patients presenting with syncope was reduced to 9% by beta-blockers and/or left cardiac sympathetic denervation. However, more recent studies point to the inadequacies of beta-blockers in high-risk patients. Dorostkar et al.⁹ found an incidence of sudden death and aborted cardiac arrest of 24% in high-risk patients (many with prior aborted sudden death, documented torsades de pointes, or failure of beta-blockers to alleviate symptoms) treated with beta-blockers and pacemakers. A study by Moss et al.¹⁰ using International Long QT Registry data also found unacceptably high mortality among high-risk LQTS patients treated with beta-blockers. Patients who were symptomatic prior to beta-blocker therapy had a 32% risk of recurrent syncope or death within 5 years on beta-blocker therapy. Patients with history of aborted cardiac arrest before beta-blocker therapy had a 14% risk of recurrent arrest within 5 years of taking beta-blockers. Considering that most of these patients are children, adolescents, or young adults without other illness, this is an unacceptably high risk, particularly in the age of the implantable cardioverter defibrillator (ICD).

In this issue of the *Journal*, Zareba et al.¹¹ report on the efficacy of ICD therapy in a high-risk LQTS population. The study by Zareba et al. is a retrospective comparison of patients in the International Long QT Registry with a history of

aborted cardiac arrest or recurrent syncope on beta-blockers, 73 of whom who received ICDs versus 161 who did not. Total mortality was 1.3% in the ICD patients over 3 years and 14% in the non-ICD patients over 8 years. Despite the difference in follow-up periods, ICD therapy was associated with a marked reduction in mortality. Although no ICD interrogation data were available in the study by Zareba et al., the authors point out that the rate of appropriate ICD discharges in a similar LQTS population reported by Groh et al.¹² was comparable to the rates of ICD discharges in MADIT and higher than those in MADIT II.

Several limitations of the study are acknowledged by the authors. Of the 17 cardiac arrest survivors who subsequently died without an ICD, 10 died within 15 days of the index cardiac arrest, raising the possibility that some of these patients may have been too sick (with postanoxic brain damage or recurrent intractable torsades de pointes) to undergo ICD implantation. Also, beta-blockers were used more frequently in the ICD patients. Nonetheless, the mortality in the non-ICD group reported by Zareba et al. is consistent with that found by Dorostkar et al.,⁹ and the very low mortality in the ICD group reported by Zareba et al. is consistent with that observed by Groh et al.¹² Thus, the retrospective study by Zareba et al. reaffirms what was strongly suspected: high-risk LQTS patients benefit from ICD therapy. Because a randomized prospective trial of ICD therapy in these patients is not possible, the study by Zareba et al. offers the best data we should expect.

It is important to recognize, however, that this report represents only a first step toward developing a broader understanding of the treatment of LQTS. As the authors point out, other subgroups of LQTS patients may benefit from ICD therapy, including those known to have *SCN5A* mutations, whose events tend to be more lethal⁵ and in whom there is less evidence for a benefit of beta-blockers,¹⁰ those with a strong family history of sudden death, and those intolerant to beta-blockers. It is because LQTS patients are young and otherwise healthy that it is so important to define the high-risk individuals so that deaths as well as the morbidity of overtreatment can be prevented.

As it has been shown to do in other high-risk groups of cardiac patients, the ICD saves lives in high-risk LQTS patients. The study by Zareba et al. supports use of the ICD in patients with prior cardiac arrest or with recurrent syncope despite use of beta-blockers. It remains to be discovered who the other high-risk LQTS patients are so that they also may benefit from life-saving ICD therapy.

References

1. Schwartz PJ: Idiopathic long QT syndrome: Progress and questions. *Am Heart J* 1985;109:399-411.
2. Moss AJ, Robinson J: Clinical features of the idiopathic long QT syndrome. *Circulation* 1992;85(Suppl I):I-140-I-144.

3. Keating MT, Sanguinetti MC: Molecular genetic insights into cardiovascular disease. *Science* 1996;272:681-685.
4. Chiang CE, Roden DM: The long QT syndromes: genetic basis and clinical implications. *J Am Coll Cardiol* 2002;36:1-12.
5. Zareba W, Moss AJ, Schwartz PJ, Vincent GM, Robinson JL, Priori SG, Benhorin J, Locati EH, Towbin JA, Keating MT, Lehmann MH, Hall WJ, for the International Long-QT Syndrome Registry Research Group: Influence of the genotype on the clinical course of the long-QT syndrome. *N Engl J Med* 1998;339:960-965.
6. Moss AJ, Zareba W, Kaufman ES, Gattman E, Peterson DR, Benhorin J, Towbin JA, Keating MT, Priori SG, Schwartz PJ, Vincent GM, Robinson JL, Andrews ML, Feng C, Hall WJ, Medina A, Zhang L, Zhiqing W: Increased risk of arrhythmic events in long-QT syndrome with mutations in the pore region of the human ether-a-go-go-related gene potassium channel. *Circulation* 2002;105:794-799.
7. Moss AJ, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, MacCluer J, Hall WJ, Weiskamp L, Vincent GM, Garson A, Robinson JL, Benhorin J, Choi S: The long QT syndrome: Prospective longitudinal study of 328 families. *Circulation* 1991;84:1136-1144.
8. Schwartz PJ, Locati E: The idiopathic long QT syndrome: Pathogenetic mechanisms and therapy. *Eur Heart J* 1985;6(Suppl D):103-114.
9. Dorostkar PC, Eldar M, Belhassen B, Scheinman MM: Long-term follow-up of patients with long-QT syndrome treated with beta-blockers and continuous pacing. *Circulation* 1999;100:2431-2436.
10. Moss AJ, Zareba W, Hall WJ, Schwartz PJ, Crampton RS, Benhorin J, Vincent GM, Locati EH, Priori SG, Napolitano C, Medina A, Zhang L, Robinson JL, Timothy K, Towbin JA, Andrews ML: Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. *Circulation* 2000;101:616-623.
11. Zareba W, Moss AJ, Daubert JP, Hall WJ, Robinson JL, Andrews M: Implantable cardioverter defibrillator in high-risk long QT syndrome patients. *J Cardiovasc Electrophysiol* 2003;14:337-341.
12. Groh WJ, Silka MJ, Oliver RP, Halperin BD, McAnulty JH, Kron J: Use of implantable cardioverter defibrillators in the congenital long QT syndrome. *Am J Cardiol* 1996;78:703-706.