First International Symposium on Long QT Syndrome on the Internet: Who benefits from ICD therapy?

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Anti-adrenergic therapy significantly reduces the risk of sudden death in LQTS. However, in some subpopulations with LQTS the risk of sudden death remains unacceptably high despite anti-adrenergic therapy. ICD implantation results in a very low risk of sudden death but may be associated with considerable emotional, social, and financial consequences, as well as a small but finite risk of operative morbidity and infection. Thus, ICD implantation is not appropriate for LQTS patients at low risk of sudden death. The challenge is to establish which LQTS patients are at high risk and, thus, likely to benefit from ICD therapy.

Since the 1970s, beta blockers and other anti-adrenergic maneuvers (such as left cervicothoracic cardiac sympathetic denervation) have been used to reduce the frequency of syncope and sudden death in LQTS.(1) In 1985, Schwartz and Locati demonstrated that antiadrenergic therapy reduced the 15-year mortality of LQTS patients presenting with syncope from >53% to 9%.(2) Beta blocking agents, together with avoidance of high-epinephrine situations and of QT-prolonging drugs, remain the mainstay of treatment of LQTS today.

More recent studies, however, have drawn attention to the inadequacies of beta blocker treatment among certain high-risk subpopulations. Dorostkar et al. found a 24% incidence of sudden death/aborted sudden death in high-risk patients (many with prior cardiac arrest, torsades de pointes, or persistent symptoms despite beta blockers) despite treatment with beta blockers and pacemakers.(3) Moss et al.(4), in a study examining data from the International Long QT Registry, discovered a 14% risk of recurrent cardiac arrest among LQTS patients with prior cardiac arrest who were treated with beta blockers. Following up on these findings, again using International Long QT Registry data, Zareba et al. (5) performed a retrospective study comparing “high risk” patients (those with history of aborted sudden death or continued syncope despite beta blocker therapy) treated with an ICD versus those treated with beta blocker therapy alone. They found that the mortality in the ICD patients was 1.3% over 3 years versus a 14% mortality over 8 years in the non-ICD patients (figure 1).

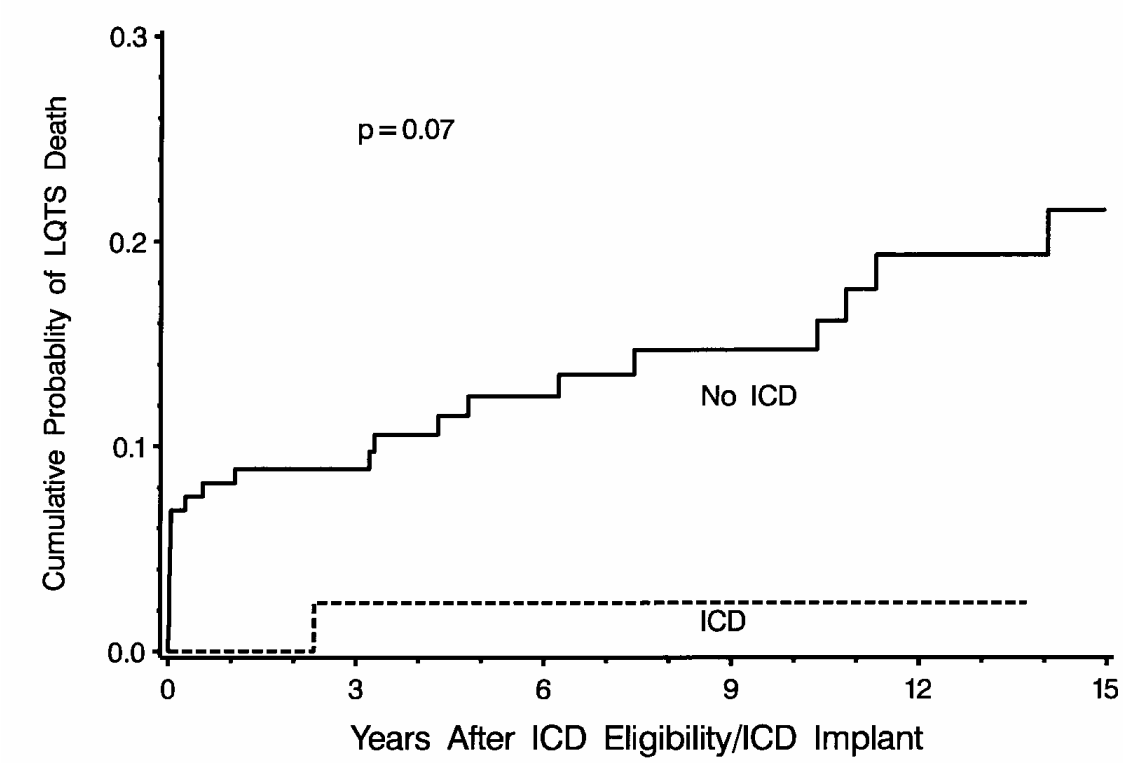

Figure 1. Cumulative probability of total death in LQTS patients with aborted cardiac arrest or recurrent syncope despite beta-blocker treatment who were treated with ICD (ICD group; n=73) and those who were not treated with ICDs (non-ICD group; n=161). In non-ICD patients, the time "zero" starts at the ICD eligibility time, which was defined as the first aborted cardiac arrest or recurrent syncope despite beta-blocker therapy. ICD implantation date was used as time "zero" in ICD group. Numbers under graph reflect number of patients in both groups at specific time points. P value is computed using the log-rank statistic.

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;14:341. Reproduced with permission from Blackwell Publishing.

During a prospective follow-up of the ICD patients, Zareba found a 6% per year risk of appropriate ICD therapy for torsades de pointes or ventricular fibrillation (figure 2).(6) Thus, there is evidence to support ICD implantation in patients with a history of aborted cardiac arrest, torsades de pointes, and persistent unexplained syncope despite beta blocker therapy.

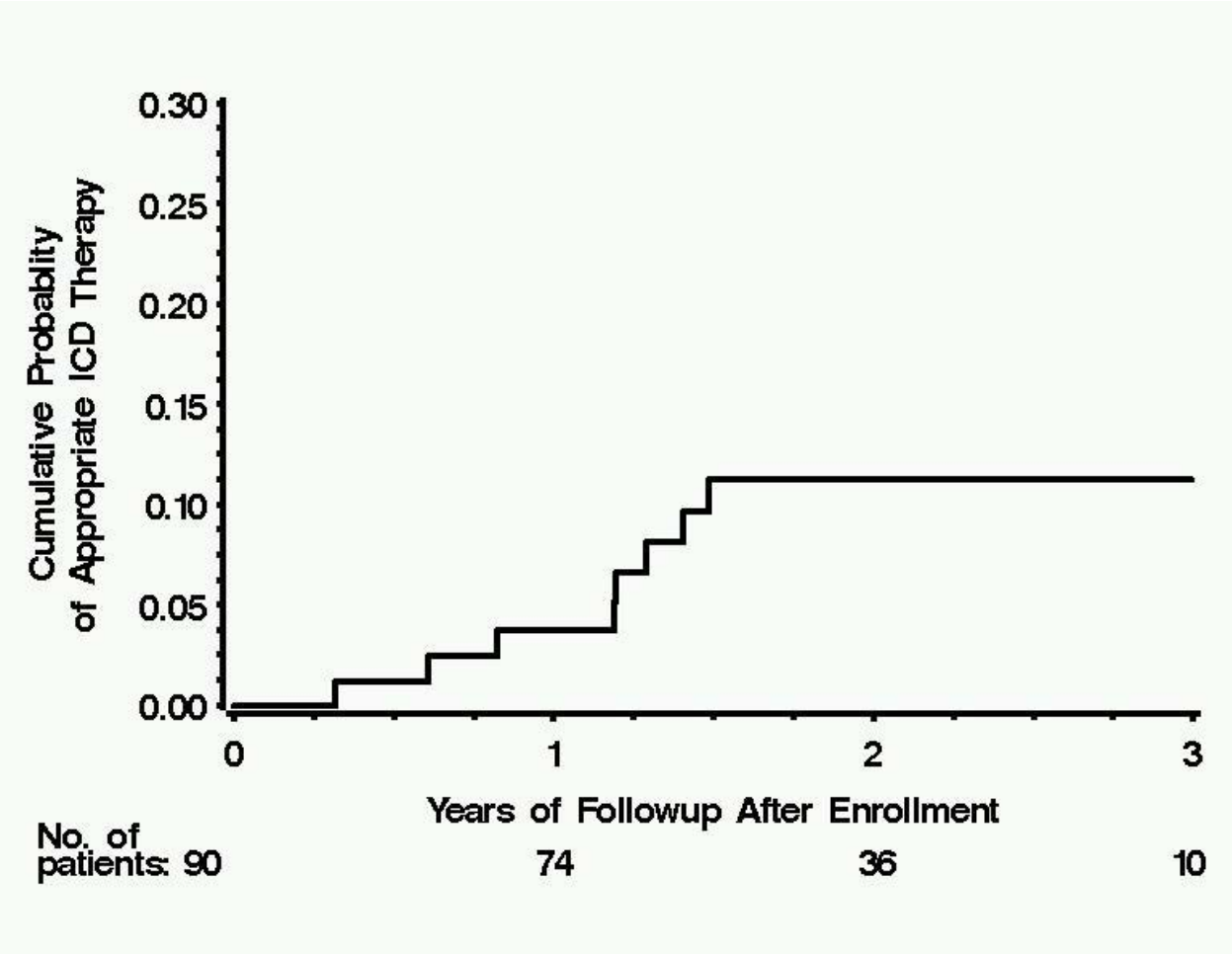

Figure 2. Cumulative Probability of Appropriate ICD Therapy in 90 LQTS Patients after Enrollment in the Rochester LQTS-ICD Registry. There were 8 (9%) patients who developed appropriate therapy for torsade de pointes or ventricular fibrillation during a prospective mean follow-up of 22 months with an appropriate ICD firing rate of approximately 6% per year (based on 11% cumulative probability during 22 months).

Zareba W, Moss AJ. Reply to editor. J Cardiovasc Electrophysiol 2003;14:1131. Reproduced with permission from Blackwell Publishing.

Other subgroups of LQTS patients appear to be at increased risk of sudden death. Although there are not yet studies comparing the efficacy of the ICD versus conventional therapies in these patients, there is a growing trend toward recommending an ICD. Such high-risk patients include a subset of patients with LQT3, patients with excessively prolonged QT intervals, and those with a strong family history of sudden death.

In patients with LQT3 (SCN5A mutations), a higher percentage of clinical events are lethal (there is less chance of “warning” syncopal episodes).(7) Furthermore, there is no convincing evidence that beta blockers reduce the risk of cardiac events in LQT3.(4) Therefore, it would seem reasonable to

consider ICD therapy for patients with LQT3 (genetically confirmed or strongly suspected on the basis of ECG morphology), particularly those with a strong family history of sudden death.

In a recent study,(8) Priori et al. examined the cumulative probability of cardiac arrest and of a cardiac event (syncope, cardiac arrest, and sudden cardiac death) before the age 40 years (and before treatment) as predicted by genotype, gender, and the QT interval. The incidence of first cardiac arrest was highest among females with LQT2 and males with LQT3. The authors reported that the risk of a first cardiac event was highest (≥ 50%) among patients with QTc ≥ 500 ms and LQT1 or LQT2, and for males with QTc ≥ 500 ms and LQT3. At intermediate risk (30-49%) were females with LQT3, males with LQT3 and QTc < 500 ms, and females with LQT2 and QTc < 500 ms. Those at lowest risk (< 30%) were patients with LQT1 and QTc < 500 ms and males with LQT2 and QTc < 500 ms. One might suppose that treatment with beta blockers would reduce the risk of cardiac events (and cardiac arrest) in the LQT1 and LQT2 subjects, but the results point to LQT3 genotype, excessive QT prolongation, and LQT2 genotype in women as markers of increased risk.

Genetic factors that influence risk are more complex than can be discerned from a simple division of LQTS patients into subtypes LQT1, 2, 3, etc. While the gene affected importantly influences the clinical syndrome, as illustrated by Priori's study, different mutations within the affected gene can result in clinical syndromes with varying severity.(9) Although detailed genetic information often is not available to the clinician, a family history that is positive for sudden death below the age of 40 years can be a marker of a more severe mutation.

In summary, current evidence supports ICD implantation in LQTS patients with a history of cardiac arrest, documented torsades de pointes, or syncope despite beta blocker therapy. Increasing evidence points toward several other high-risk subgroups who will likely derive benefit from ICD therapy. These include patients with LQT3 (especially males), females with LQT2 (especially those with QTc ≥ 500 ms), patients with especially marked QT prolongation, and patients with a malignant family history.

The ACC/AHA/NASPE 2002 guidelines for ICD implantation (10) include several recommendations relevant to LQTS patients. History of cardiac arrest or sustained VT is a Class I indication for ICD implantation. "Familial or inherited conditions with a high risk for life-threatening ventricular tachyarrhythmias such as long-QT syndrome or hypertrophic cardiomyopathy" are a Class IIb indication for ICD implantation. These guidelines open the door for ICD implantation in LQTS patients but require the clinician to decide which patients are at high risk. Further research on risk assessment and on ICD efficacy in the LQTS population will help the clinician to make this decision appropriately.

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