

Implantable Cardioverter Defibrillator in High-Risk Long QT Syndrome Patients

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ICD in High-Risk LQTS Patients. *Introduction:* Implantable cardioverter defibrillators (ICDs) are increasingly being used in high-risk long QT syndrome (LQTS) patients, but there are limited data regarding clinical experience with this therapeutic modality. The aim of this study is to describe the clinical characteristics of 125 LQTS patients treated with ICDs compared with LQTS patients having similar risk indications who were not treated with ICDs.

Methods and Results: Among 125 LQTS patients with ICDs, there were 54 cardiac arrest survivors, 19 patients who had ICDs implanted due to recurrent syncope despite beta-blocker therapy, and 52 patients with ICDs implanted due to other reasons, including syncope and LQTS-related sudden death in a close family member. Patients with cardiac arrest and those with recurrent syncope despite beta-blocker therapy ($n = 73$) were compared to 161 LQTS patients who had similar indications (89 cardiac arrest and 72 recurrent syncope despite beta-blocker therapy) but did not receive ICDs. Total mortality was the endpoint of the analysis. There was 1 (1.3%) death in 73 ICD patients followed an average of 3 years, whereas there were 26 deaths (16%) in non-ICD patients during mean 8-year follow-up ($P = 0.07$ from log rank test from Kaplan-Meier curves).

Conclusion: ICDs provide an important therapeutic option to prevent sudden arrhythmic death in high-risk LQTS patients. A long-term prospective study is needed to determine the benefit of this therapeutic modality in LQTS patients. (*J Cardiovasc Electrophysiol*, Vol. 14, pp. 337-341, April 2003)

long QT syndrome, death sudden, defibrillation, prognosis

The long QT syndrome (LQTS) is an inherited disorder caused by mutations of genes encoding structure of cardiac ion channels. This disorder is associated with prolongation of the QTc interval on ECG and a propensity to cardiac events, defined as syncope, aborted cardiac arrest, or sudden cardiac death.¹⁻⁵ Beta-blockers have been used as standard therapeutic and preventive measures in LQTS.^{1,6,7} Our recent data indicate that beta-blocker treatment is effective in about 70% of LQTS patients, but 30% of patients remain at increased risk for cardiac events despite beta-blocker therapy.⁷ LQTS patients who have already had one cardiac arrest (aborted by successful defibrillation and resuscitation) are at extremely high risk for recurrent cardiac arrest or death within a 5-year period, with a cumulative probability of aborted cardiac arrest or cardiac death of about 13% despite treatment with beta-blockers.⁷ This risk is even higher for children younger than 10 years.⁷ Patients with repeated syncopal episodes also are at increased risk for aborted cardiac arrest or death. Pacemakers are helpful in addition to beta-blocker therapy; however, this combination therapy does not prevent sudden death in LQTS

patients who continue to have cardiac events despite paced rhythm at higher than usual heart rate and beta-blockers.^{8,9}

Implantable cardioverter defibrillators (ICDs) are increasingly being used in high-risk LQTS patients, but there are limited data regarding clinical experience with this therapeutic modality.¹⁰⁻¹² In this report, we describe the clinical characteristics of 125 LQTS patients treated with ICDs. We also describe a retrospective comparison of the long-term follow-up of high-risk LQTS patients who were treated with ICDs versus those with similar risk indications who were not treated with ICDs.

Methods

Study Population

Among subjects enrolled by the Rochester, New York, enrolling center of the International LQTS Registry,¹ 125 LQTS patients were retrospectively identified as having cardioverter defibrillators implanted at the discretion of the patient's physician in numerous referral centers in the United States. Clinical information about patients enrolled in the registry was obtained using prespecified data forms, with follow-up information acquired annually. Cardiac events were defined as syncope or cardiac arrest. The baseline ECG was used for QTc and heart rate measurements. There was no access to data on interrogation of devices in the current database.

Indications for ICD therapy were categorized according to the history preceding ICD implantation. They included aborted cardiac arrest, recurrent syncope despite beta-blocker treatment, and other indications. Although aborted cardiac

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arrest and recurrent syncope despite beta-blocker treatment seem to be clinically acceptable indications for ICD placement, there are numerous LQTS patients who experienced aborted cardiac arrest or recurrent syncope on beta-blockers but were not treated with ICD therapy. To determine the effectiveness of ICD therapy in LQTS patients, we compared the clinical course of the disease between LQTS patients with ICD implanted due to aborted cardiac arrest and LQTS patients, enrolled in the registry, with a history of aborted cardiac arrest who have not been treated with ICDs. In addition, we compared the clinical course of LQTS patients with ICDs implanted due to recurrent syncope despite beta-blocker therapy with LQTS patients, from the registry, with recurrent syncope despite beta-blocker therapy who did not receive ICDs. The non-ICD groups for these comparisons included all (without exclusion) LQTS patients from Rochester enrollment of LQTS patients in the International LQTS Registry, meeting the ICD eligibility criteria (aborted cardiac arrest or recurrent syncope despite beta-blocker therapy).

Endpoints and Follow-Up

Similar to other ICD studies, total mortality was the endpoint of the analysis. We did not have access to information from ICD interrogation; therefore, we could not determine the occurrence and appropriateness of ICD shocks and other device modalities (antitachycardia pacing and other pacemaker options).

For comparison of the clinical course of the disease in ICD and non-ICD patients, the ICD eligibility time was defined as the first aborted cardiac arrest or recurrent syncope despite beta-blocker therapy for the two ICD indication groups, respectively. For non-ICD patients, follow-up started from the eligibility time, whereas for ICD patients it started from ICD implantation date. The period between eligibility time and ICD implantation date, in the ICD group, was not included in the analysis.

Statistical Analysis

Comparisons of clinical variables between ICD and non-ICD patients were performed using a conditional binomial test for comparing two counts, *t*-test for comparing two means, and Mann-Whitney test for comparing two sets of rates. The cumulative probability of LQTS death was estimated using the method of Kaplan and Meier with a log rank test for significance.

Results

Clinical Characteristics of LQTS Patients with ICDs

As shown in Table 1, LQTS patients with ICDs were dominated by females (73%) and by probands (84%), with mean age at first cardiac event of 15 years. Age at ICD implantation was 23 years on average (range <1 to 40 years). Almost all patients with ICDs (94%) had cardiac events defined as syncope or aborted cardiac arrest, and 43% had aborted cardiac arrest. Based on the clinical history, we identified two subgroups with clear ICD indications: LQTS patients with aborted cardiac arrest (*n* = 54) and those with recurrent syncope despite beta-blocker treatment (*n* = 19). The remaining 52 (42%) patients had a variety of other indications, including one or more untreated syncopal episodes, single syncopal episodes treated with beta-blockers (84%), or sudden death

TABLE 1
Clinical Characteristics of 125 LQTS Patients with ICDs

	ICD Patients (<i>n</i> = 125)
Clinical History	
Females	91 (73)
Age at first cardiac event (years)	15 ± 10
Age at ICD implantation (years)	23 ± 10
≤10 years (M/F)	8/4
≤15 years (M/F)	17/17
≤20 years (M/F)	25/33
>20 years (M/F)	9/58
Probands	105 (84)
Congenital deafness	7 (6)
Family history of LQTS death	30 (24)
Any cardiac events	117 (94)
Aborted cardiac arrest	54 (43)
ECG	
RR (msec)	858 ± 207
QTc (msec)	517 ± 57
Documented torsades de pointes	23 (18)
Genotype*	
LQT1	8 (6)
LQT2	12 (10)
LQT3	6 (5)
Treatment Prior to ICD	
Beta-blockers	103 (82)
Pacemakers	33 (26)
Left cervicothoracic ganglionectomy	9 (7)
Indications for ICD	
Aborted cardiac arrest	54 (43)
Recurrent syncope despite beta-blocker treatment	19 (15)
Other indications	52 (42)
Syncope (<i>n</i> = 44)	
Sudden death in family (<i>n</i> = 16)	

*Genotype based on genetic testing of the individual or family member was known in 26 patients.

F = female; ICD = implantable cardioverter defibrillator; LQTS = long QT syndrome; M = male.

in a close family member (31%) usually associated with long QTc (520 ± 57 msec on average). More than one of these conditions could exist simultaneously.

When comparing the distribution of ICD implants by age and gender, we found that 34 (27%) LQTS patients (17 male and 17 female) had ICDs implanted when they were younger than 16 years. In the group of 91 patients who were 16 years and older, there was a predominance of females (74 females and 17 males; *P* < 0.001). ICDs were implanted at age less than 20 years in 58 (46%) patients and less than 10 years in 12 (10%) patients; the youngest child had an ICD implanted at age 1 year.

LQTS genotype was known based on genetic testing of an individual or a family member in 26 patients, including 8 LQT1, 12 LQT2, and 6 LQT3 patients. Aborted cardiac arrest was an indication for ICD in 2 LQT1, 6 LQT2, and none of the LQT3 patients.

Long-Term Follow-Up and Mortality in ICD Patients

Mean follow-up after ICD was 3 ± 3 years (range 0–13). There were 2 (1.6%) deaths in 125 ICD-treated LQTS patients. The first was a 6-year old boy, with QTc ranging between 0.54 and 0.64 seconds, who died during general anesthesia for a dental procedure. Death was due to incessant torsades de pointes. At age 2 months, he underwent left

cervicothoracic stellectomy and placement of a VVI pacemaker (due to second-degree AV block). During his lifetime he had a few syncopal episodes despite beta-blocker treatment. On multiple occasions, he also had recorded T wave alternans. He had syndactyly. There was no sudden death in his family. At age 4 years, he received an ICD with subsequent reimplantation (for unknown reasons) at age 6 years. Before the fatal event, he was treated with propranolol 105 mg/day (>4 mg/kg).

The second death in a patient with an ICD was a suicide in a 21-year old woman, with QTc ranging between 0.44 and 0.46 seconds. The patient was a member of a genetically confirmed LQT3 family (*SCN5A* sodium channel gene mutation) in which three sisters died from the disorder. The patient had no history of cardiac events, and she was taking prophylactic propranolol 120 mg/day. The ICD was implanted at age 20 years, after her third sister died.

Comparison of LQTS Patients with Aborted Cardiac Arrest Treated and Not Treated with ICD

In Rochester enrollment in the International LQTS Registry, there were 143 LQTS patients with aborted cardiac arrest, 54 (38%) of whom were treated with ICDs. Baseline characteristics of these groups were similar (Table 2). Clinical comparison of these 54 ICD patients and the remaining 89 non-ICD patients (Table 2) showed that their cardiac arrest occurred at similar ages (20–21 years on average), they were of similar ages at their first cardiac event, and they had similar cardiac event rates before aborted cardiac arrest. Compared with non-ICD patients, LQTS patients who received ICDs more frequently were probands, although they have similarly

prolonged QTc duration. ICD patients were treated more aggressively before their first aborted cardiac arrest. Time from last cardiac arrest to ICD implantation was <1 month in 67% of the patients, 1 to 12 months in 11%, and >12 months in 22%.

Mean follow-up was markedly longer in non-ICD than ICD patients (9 vs 3 years), during which there were 17 deaths in the non-ICD group and no deaths in the ICD group.

Comparison of LQTS Patients with Recurrent Syncope Despite Beta-Blocker Treatment With and Without ICDs

Among 91 LQTS patients with recurrent syncopal episodes despite beta-blocker treatment, there were 19 (21%) patients who received ICDs (Table 3). The ICD and non-ICD patients were at similar ages when they had their first cardiac event and when they had their recurrent syncope despite beta-blocker treatment. Of note, they were younger than patients with aborted cardiac arrests (Table 2) at their clinical presentation. Compared with non-ICD patients, ICD patients with recurrent syncope were treated more aggressively before eligibility time with pacemakers (58%) and stellectomy (16%). Mean follow-up again was longer in non-ICD than ICD patients (7 vs 4 years), during which there were 9 deaths in the non-ICD group and 1 death in the ICD group.

Figure 1 shows the cumulative probability of LQTS death in 73 ICD patients versus 161 non-ICD patients with aborted cardiac arrest or recurrent syncope despite beta-blocker treatment. At the 3-year time point (which was a mean follow-up for ICD patients), the cumulative risk of sudden death was 2% in the ICD arm and 9% in the non-ICD arm. This difference widened over time. Among 52 patients with other

TABLE 2
Comparison of Clinical Characteristics of LQTS Patients with Aborted Cardiac Arrest who Did and Did Not Receive ICDs

	Non-ICD Patients (n = 89)	ICD Patients (n = 54)	P Value
Females	72 (81)	42 (78)	
Age at eligibility for ICD (years)	20 ± 10	21 ± 10	
Age at first cardiac event (years)	16 ± 10	16 ± 10	
Age at ICD implantation (years)	–	23 ± 9	
Probands	65 (73)	51 (94)	0.002
Family history of LQTS death	18 (20)	6 (11)	
Clinical Characteristics Before ICD Eligibility			
Patients with cardiac event rate per patient per year ≥ 1	5 (6)	5 (10)	
ECG			
RR (msec)	842 ± 218	828 ± 199	
QTc (msec)	512 ± 63	520 ± 60	
Documented torsades de pointes	6 (7)	12 (22)	0.025
Treatment			
Beta-blockers	14 (16)	40 (74)	<0.001
Pacemakers	2 (2)	10 (19)	0.003
Left cervicothoracic stellectomy	0	5 (9)	0.015
Clinical Characteristics After ICD Eligibility			
Follow-up time (years)	9 ± 7	3 ± 3	<0.001
Patients with cardiac events*	49 (55)	9 (17)	
Patients with cardiac event rate per patient per year ≥ 1	14 (16)	4 (7)	
Aborted cardiac death	10 (11)	2 (4)	
LQTS death	17 (19)	0	<0.001
Treatment			
Beta-blockers	66 (74)	49 (91)	0.015
Pacemakers	17 (19)	7 (13)	
Left cervicothoracic stellectomy	14 (16)	1 (2)	0.016

*Counts of patients with cardiac events are not statistically different after adjustment for different group size and differences in follow-up. ICD = implantable cardioverter defibrillator; LQTS = long QT syndrome.

TABLE 3

Comparison of Clinical Characteristics of LQTS Patients with Recurrent Syncopal Episodes Despite Beta-Blocker Treatment Who Did and Did Not Receive ICDs

	Non-ICD Patients (n = 72)	ICD Patients (n = 19)	P Value
Females	40 (56)	13 (68)	
Age at eligibility for ICD (years)	16 ± 9	14 ± 10	
Age at first cardiac event (years)	9 ± 8	8 ± 6	
Age at ICD implantation (years)	–	15 ± 10	
Probands	49 (68)	15 (79)	
Family history of LQTS death	30 (42)	8 (42)	
Clinical Characteristics Before ICD Eligibility			
Patients with cardiac event rate per patient per year ≥ 1	18 (29)	2 (11)	
ECG			
RR (msec)	875 ± 240	786 ± 189	
QTc (msec)	508 ± 65	501 ± 53	
Documented torsades de pointes	6 (8)	3 (16)	
Treatment			
Beta-blockers	72 (100)	19 (100)	
Pacemakers	3 (4)	11 (58)	<0.001
Left cervicothoracic stellectomy	1 (1)	3 (16)	0.061
Clinical Characteristics After ICD Eligibility			
Follow-up time (years)	7 ± 6	4 ± 3	0.003
Patients with cardiac events*	48 (67)	5 (26)	0.002
Patients with cardiac event rate per patient per year ≥ 1	10 (14)	0	<0.001
Aborted cardiac death	2 (3)	0	
LQTS death	9 (13)	1 (5)	
Treatment			
Beta-blockers	68 (94)	18 (95)	
Pacemakers	20 (28)	2 (11)	
Left cervicothoracic stellectomy	9 (13)	0	

*Counts of patients with cardiac events are not statistically different after adjustment for different group size and differences in follow-up. ICD = implantable cardioverter defibrillator; LQTS = long QT syndrome.

indications for ICD, there was one suicidal death (described earlier).

Discussion

This study involves the largest cohort to date of LQTS patients treated with ICDs. ICDs were implanted in high-risk LQTS patients as defined by history of cardiac events in 117 (94%) of 125 patients, with 53 (43%) patients having had a prior cardiac arrest. The ICD cohort had substantial prolongation of ventricular repolarization and high beta-blocker and pacemaker use prior to ICD implantation. During a mean 3-year follow-up, only two patients died, one with incessant TdP and the other by suicide.

Because it is not possible to run a randomized trial in high-risk LQTS patients who have an approved indication for ICD (those with cardiac arrest and recurrent syncope despite beta-blocker therapy), we chose to use historical controls, that is, LQTS patients from the registry who met similar requirements but did not receive ICDs. During long-term follow-up of 161 high-risk patients who did not receive an ICD, there were 26 (16%) sudden deaths. In contrast, there was only 1 (1%) death among comparable 73 ICD patients. Despite significant differences in follow-up between ICD and comparison non-ICD groups (3 and 8 years on average, respectively), there is evidence for a marked reduction in the risk of death by ICD. With just one death in the ICD group compared with non-ICD patients matched for indications, it is difficult to quantify the reduction in mortality that could be attributed to the ICD. Projecting the numbers from Kaplan-Meier curves for a 3-year period, we observed 2% mortal-

ity in ICD patients and 9% mortality in non-ICD patients. The difference became more marked with longer follow-up ($P = 0.07$).

Limitations of the study include the retrospective nature of the analysis and lack of interrogation data from devices documenting their appropriate use. All previously published studies reporting on the use of ICD in LQTS patients have used retrospective data or information about single cases of treated patients.¹⁰⁻¹² Groh et al.¹² analyzed the manufacturer data on ICDs implanted in LQTS patients. They found that among 35 patients studied, during a mean 3-year follow-up there were no deaths and there were 21 patients who had appropriate therapy delivered by the device (mean ICD discharges 1.2 ± 2.3 per patient per year). Silka et al.¹¹ described a similar ICD discharge rate in 14 pediatric LQTS patients, emphasizing that this patient population likely would benefit from ICD therapy as much as older patients. This high rate of the appropriate ICD therapy is comparable with respective rates in hypertrophic cardiomyopathy patients.¹³

The risk of cardiac events in LQTS seems to be the highest in adolescence.¹⁴ One fourth of our LQTS-ICD cohort had ICDs implanted at age less than 16 years; the youngest ICD recipient was 1 year old. As expected,¹⁵ males and females were equally distributed below age 16 years; males predominated at a younger age, whereas females dominated the pool of ICD patients in adulthood. This relatively large proportion of children indicates an increasing trend toward implantation of ICDs at a younger age to prevent sudden death.

The ICDs in LQTS patients could be associated with potential problems, including electrical storms (arrhythmias and ICD shock might beget enhanced sympathetic tone and

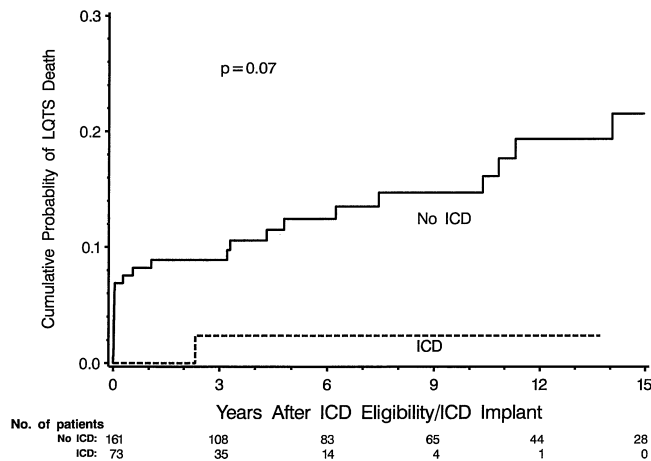


Figure 1. Cumulative probability of total death in long QT syndrome (LQTS) patients with aborted cardiac arrest or recurrent syncope despite beta-blocker treatment who were treated with an implantable cardioverter defibrillator (ICD group; $n = 73$) and those who were not treated with an ICD (non-ICD group; $n = 161$). In non-ICD patients, 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 the ICD group. Numbers under the graph reflect the number of patients in the two groups at specific time points. P value was computed using the log rank statistic.

further arrhythmias), T wave oversensing, and need for lifetime ICD protection requiring reimplantations with possible complications.¹⁶⁻¹⁸ We did not evaluate those aspects of ICD therapy in this study, given its retrospective nature. Our retrospective analysis could have overestimated the benefit of ICDs in the patients studied given the shorter follow-up of ICD patients than non-ICD controls, more frequent use of beta-blockers in ICD patients, and lag time between cardiac events and implantation, making it difficult to compare ICD patients with retrospectively analyzed non-ICD patients. Some of the non-ICD patients could have complications of cardiac arrest that could have precluded them from qualifying for ICD therapy. All of these limitations point to the need for a long-term prospective study to determine the benefit of this therapeutic modality in LQTS patients.

Conclusion

Similar to other inheritable disorders, including hypertrophic cardiomyopathy,¹⁴ Brugada syndrome,¹⁹ and arrhythmogenic right ventricular cardiomyopathy,²⁰ ICD therapy provides an important therapeutic option to prevent sudden arrhythmic death in LQTS patients. Most LQTS patients have implanted ICDs as a secondary preventative measure after experiencing cardiac arrest or recurrent syncope despite conventional treatment. However, there are subgroups of LQTS patients who might benefit from primary prevention with ICD therapy implemented prior to first cardiac event, including patients with *SCN5A* gene mutations who have a particularly high mortality from cardiac events,⁴ and those with *HERG* gene mutations in the pore region, who have an 11-fold higher risk of cardiac events than those with mutations not in the pore region.²¹ Further studies are needed to evaluate the usefulness of ICDs in these subgroups.

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