Effectiveness and Limitations of β-Blocker Therapy in Congenital Long-QT Syndrome

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Background—β-blockers are routinely prescribed in congenital long-QT syndrome (LQTS), but the effectiveness and limitations of β-blockers in this disorder have not been evaluated.

Methods and Results—The study population comprised 869 LQTS patients treated with β-blockers. Effectiveness of β-blockers was analyzed during matched periods before and after starting β-blocker therapy, and by survivorship methods to determine factors associated with cardiac events while on prescribed β-blockers. After initiation of β-blockers, there was a significant ($P<0.001$) reduction in the rate of cardiac events in probands (0.97 ± 1.42 to 0.31 ± 0.86 events per year) and in affected family members (0.26 ± 0.84 to 0.15 ± 0.69 events per year) during 5-year matched periods. On-therapy survivorship analyses revealed that patients with cardiac symptoms before β-blockers (n=598) had a hazard ratio of 5.8 (95% CI, 3.7 to 9.1) for recurrent cardiac events (syncope, aborted cardiac arrest, or death) during β-blocker therapy compared with asymptomatic patients; 32% of these symptomatic patients will have another cardiac event within 5 years while on prescribed β-blockers. Patients with a history of aborted cardiac arrest before starting β-blockers (n=113) had a hazard ratio of 12.9 (95% CI, 4.7 to 35.5) for aborted cardiac arrest or death while on prescribed β-blockers compared with asymptomatic patients; 14% of these patients will have another arrest (aborted or fatal) within 5 years on β-blockers.

Conclusions—β-blockers are associated with a significant reduction in cardiac events in LQTS patients. However, syncope, aborted cardiac arrest, and LQTS-related death continue to occur while patients are on prescribed β-blockers, particularly in those who were symptomatic before starting this therapy. **(*Circulation*. 2000;101:616-623.)**

Key Words: arrhythmia ■ syncope ■ death, sudden ■ heart arrest ■ long-QT syndrome

The congenital long-QT syndrome (LQTS) is a familial disorder in which affected individuals have prolonged ventricular repolarization, frequent syncopal episodes, and a propensity to sudden arrhythmic cardiac death.[1] Syncope and sudden death may be precipitated by acute arousal,[2] and β-blockers have become standard prophylactic therapy.[3,4] Other forms of therapy have included pacemakers to prevent bradycardia-induced ventricular tachyarrhythmias,[5] surgical antiadrenergic therapy with left cervicothoracic sympathetic ganglionectomy,[6,7] and implantable cardioverter defibrillators (ICD) in LQTS patients refractory to more conservative therapy.[8]

There has never been a randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of β-blockers in LQTS. It would be difficult to carry out a randomized trial with β-blockers in LQTS at this time because of the apparent clinical efficacy of β-blockers in this disorder.[4] This study was undertaken to investigate the clinical effectiveness of β-blockers in LQTS patients enrolled in the International LQTS Registry and to evaluate risk factors for syncope, aborted cardiac arrest, and death during prescribed β-blocker therapy.

Methods

Study Population

The study population was drawn from the International LQTS Registry and involved 730 proband-identified families. All affected

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TABLE 1. Clinical Characteristics of LQTS Probands and Affected Family Members

	Probands (n=581)	Affected Family Members (n=288)
Demographics		
Age at first cardiac event,* y	12±9	11±8
Age β-blockers started, y	16±11	15±12
Sex, F (%)	69	49
History		
Congenital deafness, %	6	1
Syncope or aborted cardiac arrest before β-blockers, %	80	32
Electrocardiogram†		
Heart rate, bpm	77±22	86±26
QTc, s	0.52±0.06	0.50±0.04
Ancillary LQTS therapy (any time), %		
Pacemaker	18	6
Left sympathetic ganglionectomy	13	2
Implanted defibrillator	7	1

Values are mean±SD where indicated.

*For patients with ≥1 cardiac event (syncope or aborted cardiac arrest).

†First recorded electrocardiogram before β-blockers (n=303 and 223 for probands and affected family members, respectively).

LQTS patients who had β-blocker therapy prescribed before 41 years of age were included. LQTS was diagnosed by prolonged QTc criteria for age and gender as previously reported.[1] Genotype data were available on 139 LQTS patients (69 *LQT1*, 42 *LQT2*, and 28 *LQT3* patients).

β-Blocker Therapy

β-blocker therapy was initiated at the discretion of each patient's attending physician. Various β-blockers were prescribed in LQTS patients enrolled from around the world. During the initial patient contact, we determined, to the extent possible, if β-blockers had been started, the specific β-blocker initiated, the date started, the prescribed dose, and the patient's weight. At subsequent yearly contacts, we recorded whether the patient continued taking β-blockers, and if so, the daily dose; if patients discontinued therapy we recorded the date stopped. Among patients who died, we retrospectively determined if the patient had been on a prescribed β-blocker before death.

TABLE 2. Prescribed Daily β-Blocker Dose in LQTS Patients

β-Blockers	Dose*	At Initiation	Last Recorded Dose†
Atenolol	mg	54±31 (141)	65±44 (167)
	mg/kg	1.1±0.7 (58)	1.3±0.8 (61)
Metoprolol	mg	118±68 (44)	121±125 (52)
	mg/kg	2.2±1.6 (22)	1.8±1.1 (22)
Nadolol	mg	55±41 (102)	79±64 (171)
	mg/kg	1.0±0.8 (45)	1.4±1.0 (82)
Propranolol	mg	77±72 (467)	108±86 (345)
	mg/kg	2.2±1.6 (232)	2.9±1.8 (169)

Values are mean±SD.

*Weight in kilograms was obtained at initiation of β-blockers in 357 patients and at last recorded dose in 329 patients.

†An average of 2.5 years after initiation of β-blockers.

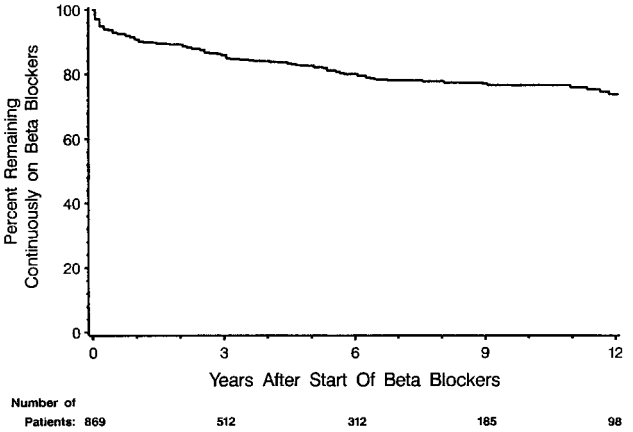

Figure 1. Percentage of patients remaining continuously on prescribed β-blockers over time after initiation of β-blocker therapy. Patients who had discontinued β-blockers for >2 days were considered off β-blockers.

LQTS-Related Cardiac Events

LQTS-related cardiac events include unexplained syncope, aborted cardiac arrest requiring cardiac resuscitation, unexpected sudden death exclusive of a known cause before age 41 years, and sudden death during LQTS-related surgery (n=1).

Data Management

Clinical data were recorded on prospectively designed forms and included patient and family history and demographic, electrocardiographic, therapeutic, and cardiac event information. The reported analyses used LQTS analytic database version 9.0 (released October 22, 1997).

Statistical Analysis

To evaluate the effect of β-blocker therapy, a matched-period analysis was performed. For each patient, periods of equal duration before and after starting β-blocker were identified, with patients serving as their own controls. The number of cardiac events, event rates per patient, and event rates per year were determined for the matched periods and aggregated or averaged over patients. The event frequencies after initiation of β-blockers were determined using both an intention-to-treat-type approach (all patients started on β-blockers were included in the subsequent matched-period analysis) and an on-treatment approach (patients were censored during the time they were known to be off β-blockers for >2 days). Numbers of cardiac events >25 for a given patient before or after starting β-blockers were counted as 25 (n=18 patients), and rates of cardiac events >5 per patient per year were treated as 5 (n=62 patients). When comparing the numbers of patients with any cardiac event before and after starting β-blockers, McNemar's χ^2 test was used. When comparing counts of cardiac events or rates of cardiac events, Wilcoxon's signed rank test was used. All *P* values are 2-sided.

To identify risk factors for cardiac events during prescribed β-blocker therapy, we used the Cox proportional hazards method.[9] The response studied was the duration of time until an end point occurred and up to 2 days after discontinuing therapy. The potential risk factors studied were demographic and clinical characteristics of patients before β-blocker therapy was initiated. To estimate the cumulative probability of events over time, the cumulative hazard method was used with a log transformation for constructing confidence limits.

Results

Population Characteristics

The pertinent clinical characteristics of the study population are presented in Table 1. Probands were predominantly

TABLE 3. Cardiac Events in Probands and Affected Family Members During Matched Periods Before and After Initiation of β-Blockers

	Before	After	P
Probands (n=581)			
QTc, s (n=221)	0.51±0.06	0.49±0.06	<0.001
Patients with any cardiac event, n (%)	462 (80)	194 (33)	<0.001
No. of cardiac events per patient	3.0±4.8	1.1±3.0	<0.001
Cardiac event rate (events per patient per year)	0.97±1.42	0.31±0.86	<0.001
Patients with aborted cardiac arrest or LQTS death, n (%)	100 (17)	50 (9)	
Patients with LQTS death, n (%)	†	10 (2)	
Affected Family Members (n=288)			
QTc, s (n=148)	0.50±0.05	0.48±0.04	0.005
Patients with any cardiac event, n (%)	92 (32)	49 (17)	<0.001
No. of cardiac events per patient	0.9±2.4	0.5±2.4	<0.001
Cardiac event rate (events per patient per year)	0.26±0.84	0.15±0.69	<0.001
Patients with aborted cardiac arrest or LQTS death, n (%)	11 (4)	11 (4)	
Patients with LQTS death, n (%)	†	10 (3)	

For 27 probands and 3 affected family members, the occurrence but not the count of cardiac events in a pre-β-blocker or β-blocker period was known; these 30 patients are omitted when the number of cardiac events was used in the analyses. Cardiac events before β-blockers include syncope or aborted cardiac arrest; cardiac events after starting β-blockers also include LQTS-related death. Values are mean±SD where indicated. The risk exposure before and after β-blockers was 5.2±4.4 years (range <0.1–19.9) for probands and 4.5±3.9 years (range <0.1–15.7) for affected family members.

†By definition of matched periods, LQTS death could not occur before β-blocker treatment.

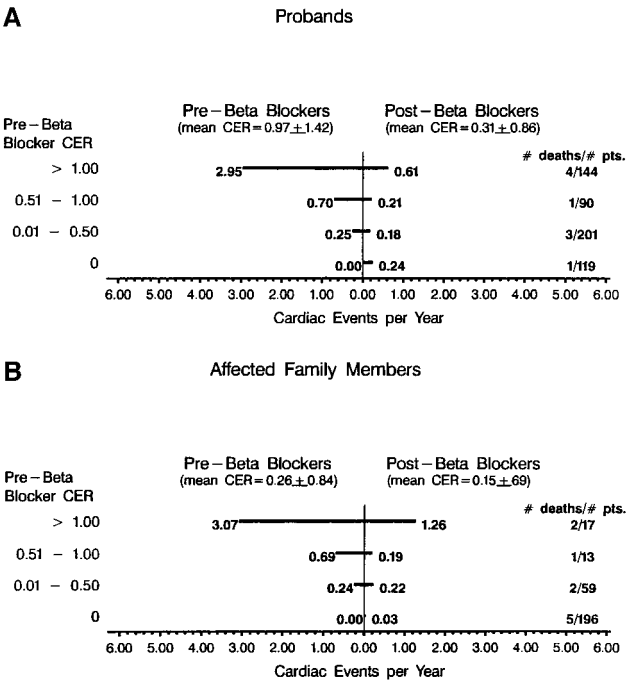

Figure 2. Mean yearly cardiac event rates (CER) during matched periods before (pre) and after (post) starting β-blockers for probands (A) and affected family members (B). The pre-β-blocker CER are subdivided into 4 ordinal categories (0; 0.01–0.50; 0.51–1.00; and >1.00). One proband who died is not included in A because the event rate in the pre-β-blocker period was not known. The length of each horizontal line reflects the mean CER before and after starting β-blockers for each CER category. The CER after β-blocker therapy is significantly reduced ($P<0.001$) in probands and affected family members.

female, had a higher frequency of congenital deafness, were more symptomatic, had slower baseline heart rates and longer QTc intervals before β-blockers, and were more likely to have received ancillary LQTS therapies than affected family members.

The dose and the dose per kilogram body weight of 4 different β-blockers prescribed at initiation of therapy and during follow-up (on average, 2.5 years later) are presented in Table 2. For the most part, there was an increase in β-blocker dosage during follow-up. The prescribed β-blocker doses were similar in probands and affected family members. The percentage of patients remaining continuously on prescribed β-blockers 5 years after initiation of therapy was 82% (Figure 1).

Cardiac Events and Cardiac Event Rates During Matched Time Periods

The average durations of risk exposure before and after starting β-blocker therapy were similar (≈5 years) in the

TABLE 4. Effect of β-Blockers on ECG Parameters by Post-β-Blocker Event Categories

	No Events (n=278)		Syncope Only (n=74)		Aborted Cardiac Arrest or Death (n=17)	
	Pre-BB	Post-BB	Pre-BB	Post-BB	Pre-BB	Post-BB
Time interval between ECGs, mo	25±32 (0.3–163)		20±28 (0.3–148)		18±23 (0.6–82)	
QT, s	0.45±0.08	0.46±0.07	0.47±0.08	0.48±0.06	0.47±0.10	0.51±0.11
RR, s	0.83±0.22	0.93±0.24	0.87±0.21	0.96±0.20	0.80±0.21	0.93±0.21
QTc, s	0.50±0.06	0.48±0.05	0.51±0.07	0.49±0.06	0.53±0.08	0.54±0.09
P*	<0.001		0.15		0.70	

*P for QTc pre- vs post-BB.

Event categories are defined by symptoms recorded during post-β-blocker periods. Values in parentheses indicate range. Pre-BB indicates pre-β-blocker; post-BB, post-β-blocker.

TABLE 5. Cardiac Events and Cardiac Event Rates for Matched Periods Before and After Initiation of β-Blockers by LQT Genotypes

Genotype	Before	After	*P*
LQT1 (n=69)			
QTc, s (n=23)*	0.52±0.05	0.50±0.04	NS
Patients with any cardiac event, n (%)	39 (57)	13 (19)	<0.001
No. of cardiac events per patient	1.4±2.6	0.3±0.7	<0.001
Cardiac event rate (events per patient per year)	0.26±0.64	0.04±0.12	<0.001
Patients with aborted cardiac arrest or LQTS death, n (%)	7 (10)	2 (3)	
Patients with LQTS death, n (%)	†	2 (3)	
LQT2 (n=42)			
QTc, s (n=16)*	0.51±0.07	0.50±0.05	NS
Patients with any cardiac event, n (%)	24 (57)	15 (36)	<0.001
No. of cardiac events per patient	3.4±5.9	1.2±3.8	<0.001
Cardiac event rate (events per patient per year)	0.46±0.78	0.16±0.36	<0.001
Patients with aborted cardiac arrest or LQTS death, n (%)	4 (10)	2 (5)	
Patients with LQTS death, n (%)	†	1 (2)	
LQT3 (n=28)			
QTc, s (n=9)*	0.53±0.05	0.53±0.05	NS
Patients with any cardiac event, n (%)	4 (14)	4 (14)	NS
No. of cardiac events per patient	0.2±0.5	0.1±0.4	NS
Cardiac event rate (events per patient per year)	0.03±0.07	0.03±0.08	NS
Patients with aborted cardiac arrest or LQTS death, n (%)	0	3 (10)	
Patients with LQTS death, n (%)	†	2 (7)	

The risk exposure before and after β-blockers was 5.9±4.6 (range <0.1–16.7) years for *LQT1*, 7.2±5.0 (<0.1–19.9) years for *LQT2*, and 5.6±4.1 (<0.1–14.1) years for *LQT3* patients. Cardiac events before β-blockers include syncope or aborted cardiac arrest; cardiac events after starting β-blockers also include LQTS-related death. Values are mean±SD where indicated.

*Number of patients available with paired ECGs before and after β-blockers.

†By definition of matched periods, LQTS death could not occur before start of β-blocker treatment.

probands and the affected family members (Table 3). β-blockers were associated with a small but significant reduction in QTc. The number of patients with cardiac events, the number of events per patient, and the event rate per patient per year were each significantly reduced ($P<0.001$) after starting β-blocker therapy in probands and in affected family members (Table 3). The reduction in the rate of cardiac events was most marked in patients with the highest pre-β-blocker event rates (Figure 2A and 2B). Ten probands and 10 family members died after starting β-blockers, with 3 probands and 2 family members having discontinued β-blockers before death.

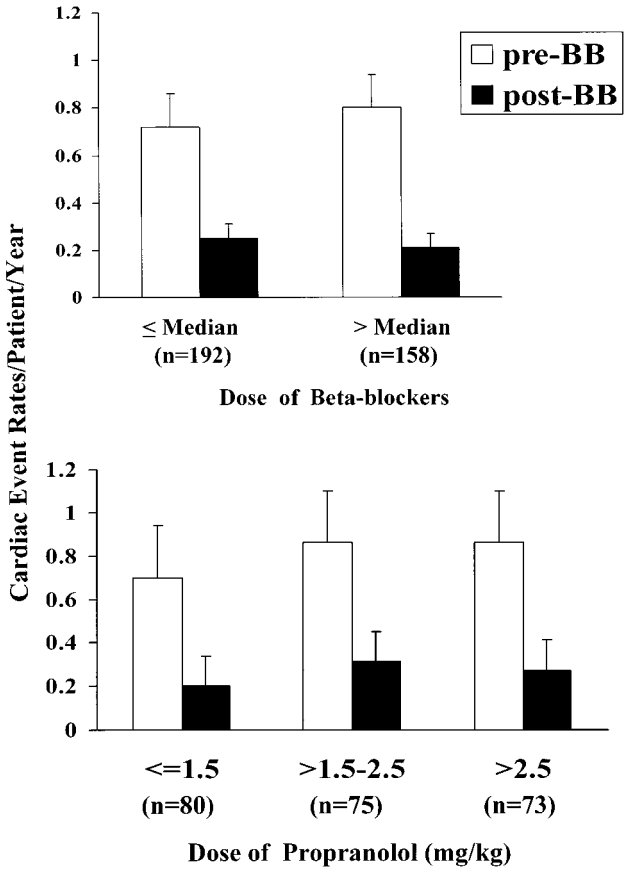

Figure 3. Top, Cardiac event rates per patient per year before (pre-BB) and after (post-BB) starting β-blockers during matched time periods for each of 4 β-blockers (atenolol, metoprolol, nadolol, and propranolol) dichotomized at their median doses (milligram per kilogram body weight per day). There were similar and significant reductions in cardiac event rates above and below the median β-blocker doses. Bottom, Cardiac event rates per year before (pre-BB) and after (post-BB) starting propranolol (3 doses: ≤1.5, 1.6 to 2.5, and >2.5 mg/kg body wt per day) during matched time periods. There were similar and significant reductions in the cardiac event rates at the 3 propranolol doses.

A limited number of patients had ECGs before and after β-blockers (Table 4). β-blockers were associated with a significant decrease in the calculated QTc interval in those who were asymptomatic after initiation of β-blockers; there was a similar but nonsignificant reduction in QTc in those who subsequently experienced syncope and a slight increase in QTc in those with subsequent aborted cardiac arrest/death (Table 4).

The β-blocker results in the subset of 139 genotyped patients are presented in Table 5. β-blocker therapy had minimal effects on QTc in all 3 genotypes but was associated with a significant reduction in events and event rates in *LQT1* and *LQT2* patients. There was no evident effect of β-blockers on events in the small number of patients with *LQT3*. Of the 5 deaths that occurred in the genotyped patients after starting β-blockers, only 1 patient (*LQT3*) had discontinued therapy before death.

The dose of β-blockers (milligrams per kilogram body weight per day) was divided at the median for each of 4

TABLE 6. Risk Factors for Cardiac Events During Prescribed β-Blocker Therapy

		Any Cardiac Event*			Aborted Cardiac Arrest or Death		
Risk factor	No. of Patients	Hazard Ratio†	95% CI‡	P	Hazard Ratio†	95% CI‡	P
Age β-blocker started							
<5 yrs	157	3.1	(4.3, 3.3)	<0.001	3.8	(1.9, 7.7)	<0.001
5–9 yrs	137	1.8	(1.2, 2.5)	<0.001	2.0	(0.9, 4.5)	0.08
≥10 yrs	575	1.0	...	...	1.0	...	...
Symptoms before β-blockers							
Asymptomatic	271	1.0	...	...	1.0	...	...
Symptomatic	598	5.8	(3.7, 9.1)	<0.001	4.9	(1.9, 12.9)	0.001
Syncope only	485	6.0	(3.8, 9.4)	<0.001	3.1	(1.1, 8.4)	0.03
ACA§	113	5.1	(2.9, 8.8)	<0.001	12.9	(4.7, 35.5)	<0.001

Other variables without significant contribution to either model included proband/affected family-member status, QTc, congenital deafness, gender, heart rate, other therapy, and family history of LQTS-related death. Patients were considered on β-blockers until 2 days after going off therapy. ACA indicates aborted cardiac arrest.

*Includes syncope, aborted cardiac arrest, or death.

†Ratio of the risk of experiencing a cardiac event during any period of time on β-blockers for patients with the factor present compared to patients in the lowest risk category (the reference group with hazard ratio set to unity by convention).

‡CI for hazard ratio.

§ACA=aborted cardiac arrest with or without syncope.

β-blockers (atenolol, metoprolol, nadolol, and propranolol), and the reductions in cardiac event rates with β-blocker doses below and above the median aggregated doses were similar (Figure 3, top). Event-rate analyses were also performed for propranolol doses at ≤1.5, 1.6 to 2.5, and >2.5 mg/kg body wt per day, with significant and similar event-rate reductions at each of 3 dosage levels (Figure 3, bottom).

Risk Factors for Cardiac Events While on Prescribed β-blockers

To evaluate factors influencing the occurrence of cardiac events while patients were on prescribed β-blockers, we used the entire pre- and post-β-blocker experience (not limited to the matched time periods) and omitted any time periods during which each patient was known to be off β-blockers for >2 days. The risk factors for experiencing any cardiac event or for aborted cardiac arrest or death while on prescribed β-blockers are presented in Table 6. Risk was higher in those with β-blocker therapy initiated at a young age. For those who experienced syncope only or aborted cardiac arrest before starting β-blockers, the hazard ratios for any cardiac event on β-blockers were similar (6.0 and 5.1, respectively, Table 6). The dominant risk factor for experiencing aborted cardiac arrest or death on β-blockers was a pre-β-blocker history of aborted cardiac arrest, with a hazard ratio 12.9 compared with those who were asymptomatic before β-blockers (Table 6). Prior syncope only was less of a risk factor, with a hazard ratio 3.1.

Variables that did not make significant contributions to the time-to-event risk models, including QTc, are listed in Table 6. Similar hazard ratios to those reported in Table 6 were found for the symptom categories when children <1 year of age at the time β-blockers were initiated (n=81) were excluded. Also, we found similar hazard ratios when comparing therapy by decades when β-blockers were started (1980–1989 versus 1990–1997).

Estimates of the cumulative probability of cardiac events and of aborted cardiac arrest or death over time on prescribed β-blockers for patients ≥10 years of age, subdivided by symptom status before β-blockers, are presented in Figure 4A and 4B. Among patients who were symptomatic before initiation of β-blockers, 32% (95% CI, 27 to 37) will have recurrent symptoms or death within 5 years while on β-blockers (Figure 4A). Among patients who had an aborted cardiac arrest before β-blockers, 14% (95% CI, 7 to 21) will have another arrest (aborted or fatal) within 5 years while on β-blockers, with almost half of the 5-years arrest events within the first 6 months after starting β-blocker therapy (Figure 4B). These percentages are increased for those <10 years old when β-blockers were initiated (Table 6).

LQTS-Related Death After Starting β-blockers

Among 33 LQTS patients who died after starting β-blockers, 20 deaths occurred during matched post-β-blocker periods and 13 afterward, with 4 patients <1 year of age dying (Table 7). Two thirds of the deaths were females. Mean baseline QTc value among fatal cases (0.53±0.06) was slightly longer than in the overall study population. β-blockers were started mostly before adolescence (mean age 9±8 years), with death on average 5 years later (mean age 14±9). Among 33 patients who died, 79% had one or more cardiac events before starting β-blockers, including 30% with one or more aborted cardiac arrests. Seventy-six percent (25 of 33) of patients had a known prescription for β-blockers at last contact before death, but their compliance in taking the β-blockers on the day of death is uncertain.

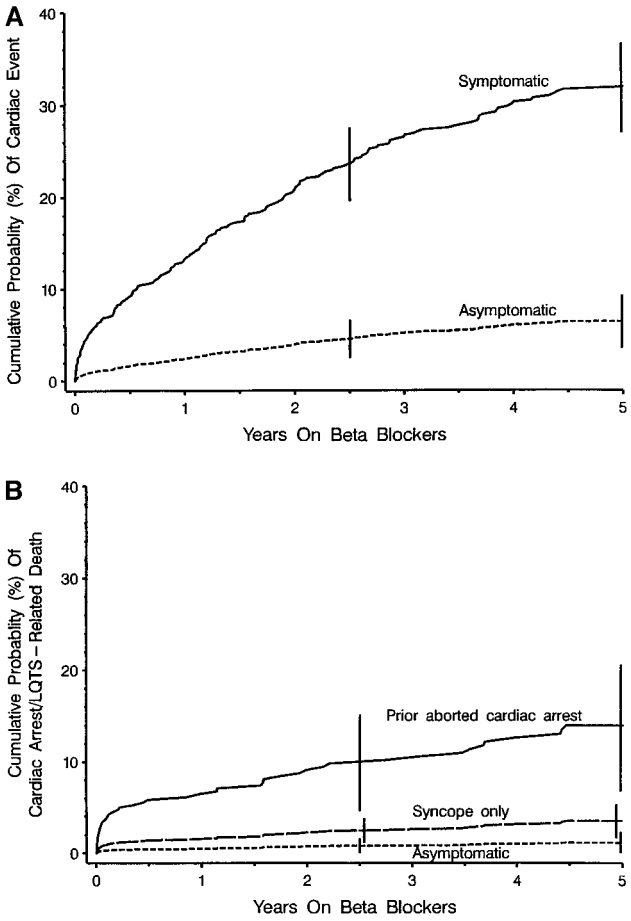

Figure 4. A, Estimated cumulative probability of experiencing syncope, aborted cardiac arrest, or LQTS-related death on prescribed β-blockers in LQTS patients who were asymptomatic (dotted line) or symptomatic (solid line) before starting β-blockers. B, Estimated cumulative probability of experiencing aborted cardiac arrest or death on β-blocker therapy in LQTS patients who were asymptomatic (dotted line), had only syncope (dashed line), or had experienced aborted cardiac arrest (solid line) before β-blockers. Vertical lines are 95% CIs. Risk curves are for LQTS patients started on β-blockers at ≥10 years of age; the risk curves are higher for those started at a younger age. Time periods off therapy for >2 days are excluded. See Table 6 for patient numbers.

Discussion

β-adrenergic blocking drugs are considered the treatment of choice in LQTS patients.[4] We found a significant reduction in the mean rate of cardiac events after starting β-blocker therapy. However, patients who had symptoms before β-blocker therapy have a high likelihood of experiencing recurrent cardiac events (32% within 5 years) despite being on β-blockers. Furthermore, 14% of patients with an aborted cardiac arrest before β-blockers are expected to experience recurrent cardiac arrest or death within 5 years while on β-blockers.

We are unable to compare the experience of patients on β-blockers to what it would have been if the patients were not treated. Reliable evaluations on this issue can come only from a randomized trial, or possibly from a retrospective matched case-control analysis. We could not perform a case-control analysis because of the limited number of high-risk patients in the Registry who were not treated with β-blockers.

There are several limitations associated with this observational, retrospective study of the LQTS Registry. β-blocker treatment was not allocated at random, thus unmeasured factors could have influenced the effects of therapy. We tried to minimize bias by using matched-period analyses before and after initiation of β-blockers, with patients serving as their own controls. This approach could introduce chronological bias if the naturally occurring cardiac event rate declines with increasing age. We found that the cardiac event rates before β-blockers were stable for patients in the 10 to 40 age range, and event analyses in this age group (data not shown) were similar to those presented in Table 6. We do not know how compliant the patients were in taking the prescribed β-blocker therapy. Some patients who died while on β-blockers may have been noncompliant in taking their prescribed medication in the 24 hours before.

The appropriate or optimal dose of β-blockers in the treatment of LQTS is uncertain. The average dose of β-blockers prescribed for LQTS patients in the Registry was somewhat below the generally recommended therapeutic dose for patients with heart disease. Although the number of patients with available data on dose of β-blockers per kilogram body weight per day is somewhat limited (Table 2), we did not observe a reduction in event rates at higher β-blocker doses (Figure 3). This unexpected lack of a dose-response effect warrants further study.

Patients with *LQT1* and *LQT2* genotypes may be more susceptible to the precipitation of ventricular tachyarrhythmias by adrenergic trigger mechanisms than patients with the rarer *LQT3* mutation. In the present study, β-blockers had similar effects in reducing cardiac event rates in *LQT1* and *LQT2* patients but did not eliminate aborted cardiac arrest or LQTS-related sudden death. Although the number of patients with *LQT3* is quite small and the event rates in this genotype are quite low, no beneficial β-blocker effect was evident in *LQT3*.

The arrhythmogenic mechanisms associated with LQTS are complex, and adrenergic phenomena are unlikely to be the sole cause of life-threatening tachyarrhythmias. The findings in Table 4 suggest that a relationship exists between β-blocking QTc shortening and reduction in cardiac events.

Our findings indicate that β-blocker therapy is not entirely effective in preventing arrhythmic sudden death in LQTS patients, possibly because of inadequate dosage, noncompliance, and/or incomplete effectiveness of β-blockers in preventing ventricular fibrillation in this disorder. ICD therapy in combination with β-blockers can be a life-saving approach in selected high-risk LQTS patients.[4,8] As shown in the present study, LQTS patients with aborted cardiac arrest before β-blocker therapy have a high likelihood of experiencing recurrent aborted cardiac arrest or death despite β-blocker therapy; we now recommend ICD therapy and β-blockers in these very high-risk LQTS patients.

TABLE 7. LQTS-Related Death After Initiation of β-Blockers in Probands and Affected Family Members

Patient	Sex	QTc (s)	Age β-Blocker Started (yrs)	Age at LQTS Death (yrs)	Cardiac Events				Dose Per Day of β-Blockers*	Other LQTS Rx†
					Before β-Blockers		After β-Blockers			
					Syn	ACA	Syn	ACA		
Probands										
1‡	M	0.45	8	13	+	−	−	+	N: 40 mg	PM, LCTSG
2‡	F	0.45	13	19	+	−	+	−	A: 150 mg	
3‡	F	0.46	7	11	+	−	−	−	P: 90 mg	
4‡	F	0.46	16	22	+	−	−	−	Off Rx	
5	F	0.46	<1	11	+	+	+	+	Off Rx	LCTSG
6‡	M	0.47	14	25	+	−	+	−	Off Rx	
7‡	F	0.47	31	32	+	−	+	−	Off Rx	PM
8‡	F	0.49	14	15	+	−	−	−	P: 135 mg	
9‡	M	0.49	12	20	+	+	−	−	N: 120 mg	
10	M	0.50	<1	<1	−	+	−	+	P: 12 mg	
11‡	F	0.53	10	15	+	−	−	−	A: 200 mg	PM
12	M	0.54	<1	7	−	−	−	−	A: 25 mg	PM
13	F	0.55	5	13	+	−	+	−	Off Rx	LCTSG
14	F	0.55	<1	6	−	−	+	−	P: 30 mg	
15	M	0.60	<1	<1	−	+	−	−	P: 30 mg	PM, LCTSG
16‡	F	0.61	<1	<1	−	−	−	−	P: 7 mg	
17	F	0.61	6	14	+	−	−	−	A: 50 mg	
18	F	0.62	<1	<1	−	−	−	−	P: 9 mg	
19	F	0.64	<1	5	−	+	−	−	P: 20 mg	LCTSG
Affected family members										
1‡	F	0.46	18	29	+	+	−	−	A: 50 mg	
2‡	F	0.50	8	13	−	−	−	−	P: 320 mg	
3‡	F	0.50	18	26	−	−	+	−	Off Rx	
4‡	M	0.50	11	14	+	−	−	−	P: Unk	
5‡	F	0.52	10	17	+	+	+	−	P: 160 mg	
6‡	F	0.52	21	28	+	+	−	−	N: Unk	
7‡	M	0.53	13	16	−	−	−	−	Off Rx	PM
8‡	F	0.54	13	13	−	+	+	−	P: Unk	
9	M	0.55	1	5	+	+	+	−	P: 80 mg	
10	F	0.57	12	32	+	−	−	−	Off Rx	
11‡	F	0.57	12	14	+	−	−	+	P: 60 mg	
12‡	M	0.58	16	23	+	−	−	−	N: 20 mg	
13§	F	0.59	1	2	+	−	+	−	P: 80 mg	
14	M	0.69	<1	6	+	−	+	−	P: 120 mg	

None of the 33 patients who died had congenital deafness or received an implanted cardioverter defibrillator.

*Last prescribed dose per day of β-blockers patients were known to be on before death. Compliance in taking the β-blockers on the day of death is uncertain. Syn indicates syncope; A, atenolol; N, nadolol; P, propranolol; Off Rx, discontinued β-blockers; Unk, unknown dose; PM, pacemaker; and LCTSG, left cervicothoracic sympathetic ganglionectomy.

†LQTS treatment (Rx) other than β-blockers.

‡Death during the matched β-blocker period (see Table 3).

§Died during anesthesia for LCTSG surgery.

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References

1. Moss AJ, Schwartz PJ, Crampton RS, Tzivoni D, Locati EH, MacCluer J, Hall WJ, Weitkamp L, Vincent M, Garson A Jr, Robinson JL, Benhorin J, Choi S. The long-QT syndrome: prospective longitudinal study of 328 families. *Circulation*. 1991;84:1136–1144.
2. Moss AJ, Robinson J. Clinical features of idiopathic long-QT syndrome. *Circulation*. 1992; 85(suppl I):I40–I44.
3. Schwartz PJ, Locati E. Idiopathic long QT syndrome: pathogenic mechanisms and therapy. *Eur Heart J*. 1985;6(suppl D):103–114.
4. Moss AJ. Management of patients with the hereditary long QT syndrome. *J Cardiovasc Electrophysiol*. 1998;9:668–674.
5. Moss AJ, Liu JE, Gottlieb S, Locati E, Schwartz PJ, Robinson JL. Efficacy of permanent pacing in the management of high-risk patients with long-QT syndrome. *Circulation*. 1991;84:1524–1529.
6. Moss AJ, McDonald J. Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long QT interval syndrome. *N Engl J Med*. 1970;285:903–904.
7. Schwartz PJ, Locati E, Moss AJ, Crampton RS, Trazzi R, Ruberti U. Left cardiac sympathetic denervation in the therapy of the congenital long-QT syndrome: a worldwide report. *Circulation*. 1991;84:503–511.
8. Groh WJ, Silka MJ, Oliver RP, Halperin BD, McAnulty JH, Kron J. Use of implantable cardioverter-defibrillator in the congenital long QT syndrome. *Am J Cardiol*. 1996;78:703–706.
9. Cox DR. Regression models and life-tables. *J R Stat Soc [B]*. 1972;34:187–220.

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