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Efficacy of Different Beta-Blockers in the Treatment of Long QT Syndrome

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ABSTRACT

BACKGROUND In LQTS, β-blocker therapy is effective in reducing the risk of cardiac events (syncope, aborted cardiac arrest, sudden cardiac death). Limited studies have compared the efficacy of different β-blockers.

OBJECTIVES The goal of this study was to compare the efficacy of different β-blockers in long QT syndrome (LQTS) and in genotype-positive patients with LQT1 and LQT2.

METHODS The study included 1,530 patients from the Rochester, New York–based LQTS Registry who were prescribed common β-blockers (atenolol, metoprolol, propranolol, or nadolol). Time-dependent Cox regression analyses were used to compare the efficacy of different β-blockers with the risk of cardiac events in LQTS.

RESULTS Relative to being off β-blockers, the hazard ratios and 95% confidence intervals (CIs) for first cardiac events for atenolol, metoprolol, propranolol, and nadolol were 0.71 (0.50 to 1.01), 0.70 (0.43 to 1.15) 0.65 (0.46 to 0.90), and 0.51 (0.35 to 0.74), respectively. In LQT1, the risk reduction for first cardiac events was similar among the 4 β-blockers, but in LQT2, nadolol provided the only significant risk reduction (hazard ratio: 0.40 [0.16 to 0.98]). Among patients who had a prior cardiac event while taking β-blockers, efficacy for recurrent events differed by drug ($p = 0.004$), and propranolol was the least effective compared with the other β-blockers.

CONCLUSIONS Although the 4 β-blockers are equally effective in reducing the risk of a first cardiac event in LQTS, their efficacy differed by genotype; nadolol was the only β-blocker associated with a significant risk reduction in patients with LQT2. Patients experiencing cardiac events during β-blocker therapy are at high risk for subsequent cardiac events, and propranolol is the least effective drug in this high-risk group. (J Am Coll Cardiol 2014;64:1352–8) © 2014 by the American College of Cardiology Foundation.

The inherited long QT syndrome (LQTS) is a genetic cardiac channelopathy resulting from delayed ventricular repolarization of cardiac cells. These changes in repolarization are detected by a prolonged QT interval on the electrocardiogram. LQTS, a relatively infrequent disorder with an estimated prevalence of 1:3 000 to 1:5 000 (1), is associated with serious cardiac events that include syncopal episodes, aborted cardiac arrest, and sudden cardiac death. The use of β-blockers in LQTS is first-line standard therapy. Although the current American College of Cardiology/American Heart Association/European Society of Cardiology guidelines recommend treatment with β-blockers in all patients with LQTS, they do not recommend 1 β-blocking agent over the others (2). Differences in pharmacodynamics and pharmacokinetics of various β-blockers are well established in terms of their selectivity in blocking β-adrenergic receptors as well as differences in adverse effects and dosing (3,4), but few clinical studies have compared the relative efficacy of different β-blockers in LQTS in general or in the major

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LQTS genotypes (LQT1 and LQT2) (5). The aim of this study was to compare the relative efficacy among the most commonly prescribed β-blockers in patients with LQTS who were enrolled in the Rochester, New York-based LQTS Registry.

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METHODS

STUDY POPULATION. The study population was drawn from the Rochester-based LQTS Registry and involved patients who were prescribed β-blockers before 40 years of age and did not have an implantable cardioverter-defibrillator (ICD) before initiation of β-blocker therapy. LQTS was diagnosed by prolonged QT interval criteria for age and sex, as previously reported (6,7) or by the presence of a genetic LQTS mutation (7). Those patients who simultaneously received 2 different β-blockers during follow-up were excluded. The study population involved 1,530 patients. The University of Rochester Medical Center Research Subjects Review Board approved this study.

TIME ORIGIN AND FOLLOW-UP. We selected the time origin as the next day after patients received their first β-blocker. Follow-up was censored when patients reached 40 years of age or had an ICD inserted, whichever occurred first. These censoring criteria were chosen to minimize the confounding influence of other cardiovascular diseases and device therapies on LQTS-related cardiac events.

PRIMARY AND SECONDARY ENDPOINTS. The primary endpoint was the occurrence of the patient's first cardiac event of any type (syncope, aborted cardiac arrest, or sudden cardiac death) *after* β-blocker initiation. The secondary endpoint was restricted to the more serious occurrence of first aborted cardiac arrest or sudden cardiac death, with syncope treated as a time-dependent covariate. The term "first cardiac event" reflects the first cardiac event happening *after* starting β-blocker therapy, regardless of prior cardiac event history.

RECURRENT CARDIAC EVENTS. In this analysis, the time origin was defined as the time when the first cardiac event occurred while taking β-blocker therapy, with similar censoring criteria at 40 years of age or at defibrillator insertion during subsequent follow-up. The term "recurrent cardiac event" reflects the *subsequent* cardiac event in patients with 1 cardiac event while taking β-blockers in reference to time origin (β-blocker initiation).

STATISTICAL ANALYSIS. This study grouped patients who started taking β-blockers into 4 categories according to their first β-blocker prescribed (atenolol, metoprolol, propranolol, or nadolol). Baseline clinical characteristics were compared by first β-blocker type using the Kruskal-Wallis test for continuous variables and chi-square tests for categorical variables. Continuous variables were summarized by the mean ± SD, and categorical variables were summarized by frequencies and proportions. Cox models were used to estimate the hazard ratio for each of the 4 time-dependent effects of β-blockers relative to patients who discontinued β-blockers after therapy initiation (8). Time-dependent analyses dynamically accounted for those patients who switched or stopped β-blocker therapy. Cox models were adjusted for age when β-blocker was started and calendar time, starting with values at therapy initiation and updating daily thereafter. Adjustment for LQTS severity was also carried out by including the following covariates: the history of cardiac events before β-blocker initiation; and the baseline QT interval measurements corrected for heart rate (QTc), with additional time-dependent covariate for syncope in the secondary endpoint analysis, that is, if syncope occurred after β-blocker therapy initiation but before the occurrence of the serious endpoint (first aborted cardiac arrest or sudden cardiac death).

The cumulative probability of a recurrent cardiac event following the first cardiac event was compared by the type of β-blocker using the Kaplan-Meier method with the log-rank test for significance. Cox regression was used to estimate the hazard ratio adjusted for the same variables as in the primary analysis, except for the history of prior cardiac events. However, unlike in typical models for multiple recurrent events, we made no assumption that the hazard ratios were identical to those for the first cardiac event. The endpoint was defined as the next occurrence of a cardiac event of any type (syncope, aborted cardiac arrest, sudden cardiac death).

Likelihood ratio tests were used to compare nested Cox-models, after using the grouped jackknife covariance estimator to verify that there was no need to account for potential dependencies as a result of family membership in inherited LQTS. All statistical tests were 2-sided 0.05 level tests. Analyses were carried out with SAS software (version 9.3, SAS Institute, Cary, North Carolina).

ABBREVIATIONS AND ACRONYMS

ICD = implantable cardioverter-defibrillator

LQTS = long QT syndrome

QTc = QT interval measurements corrected for heart rate

RESULTS

BASELINE CLINICAL CHARACTERISTICS. We studied 1,530 patients with LQTS who were started on 1 of 4 different β-blockers. More patients were started

TABLE 1 Clinical Characteristics of Patients With LQTS According to First β-Blocker Therapy*

	Atenolol (n = 441)	Metoprolol (n = 151)	Propranolol (n = 679)	Nadolol (n = 259)	p Value†
Demographics					
Age at first β-blocker, yrs	16 ± 10	24 ± 10	11 ± 11	18 ± 11	<0.001
Female sex: number, %	254 (58)	105 (70)	412 (61)	149 (58)	0.06
Calendar year of first β-blocker	1,998 ± 6	1,999 ± 6	1,993 ± 9	1,997 ± 8	<0.001
History					
Syncope or aborted cardiac arrest before first β-blocker	188 (43)	85 (56)	334 (49)	130 (50)	0.02
Family history of LQTS	76 (17)	20 (13)	148 (22)	52 (20)	0.06
ECG					
QTc-interval value, ms‡	492 ± 49	496 ± 52	500 ± 58	490 ± 51	0.13
RR interval value, ms‡	803 ± 218	842 ± 212	753 ± 247	863 ± 231	<0.001
Therapy before β-blocker					
Pacemaker before first β-blocker	15 (3)	5 (3)	31 (5)	8 (3)	0.64
Initial β-blocker doses					
Adults age 18 yrs old or older, mg/day	49 ± 29	70 ± 49	117 ± 105	54 ± 46	NA
Children younger than age 18 yrs, mg/day	40 ± 27	53 ± 47	52 ± 54	38 ± 30	NA
Adults age 18 yrs old or older, mg/kg/day§	0.7 ± 0.3	1.2 ± 0.9	2.1 ± 2.3	1 ± 0.8	NA
Children younger than age 18 years, mg/kg/day‖	1.0 ± 0.7	1.4 ± 1.0	2.3 ± 1.5	1.0 ± 0.8	NA

*Values are mean ± SD or n (%). †The p values are based on the Kruskal-Wallis test and refer to the significance of the difference across the 4 β-blocker groups. ‡First recorded QTc and RR values (baseline) in LQTS Registry. §Number of patients aged 18 years or older whose dose and weight at the initiation of β-blocker therapy were available (n = 157). ‖Number of patients younger than 18 years of age whose dose and weight at the initiation of β-blocker therapy were available (n = 379).

ECG = electrocardiogram; LQTS = long QT syndrome; NA = p values not applicable.

on propranolol (44%), compared with atenolol (28%), nadolol (17%), and metoprolol (10%). Baseline characteristics, compared by type of first β-blocker initiated, are shown in Table 1. Initial β-blocker doses calculated for patients started at 18 years of age or older and for those started before 18 years of age are also shown. Propranolol was started at a younger age and at an earlier calendar year than the other β-blockers, nadolol was associated with the slowest baseline heart rate, and approximately 50% of the patients experienced a cardiac event before the start of β-blockers.

MULTIVARIATE TIME-DEPENDENT ANALYSES: FIRST CARDIAC EVENTS IN THE GENERAL POPULATION. Cardiac events for each time-dependent β-blocker and results from the covariate-adjusted Cox models are shown in Table 2. Hazard ratios are reported relative to discontinuing β-blockers after therapy initiation. In the overall LQTS population, there was insufficient evidence of differences among the 4 β-blockers in preventing either first cardiac events or the more serious cardiac events in the study population (3-df likelihood ratio test p = 0.19 and p = 0.16, respectively).

MULTIVARIATE TIME-DEPENDENT ANALYSES: FIRST CARDIAC EVENTS IN LQT1 AND LQT2. In LQT1, the risk reduction for any β-blocker was 57% ($p < 0.01$), with insufficient evidence of differential efficacy by drug (likelihood ratio test p = 0.83) (Table 3). All 4 β-blockers were similarly protective, and risk reduction efficacy ranged from 50% to 62%. In LQT2, there was significant variability in efficacy by drug (likelihood ratio test p = 0.04), with nadolol being the only β-blocker showing a significant reduction in the risk of cardiac events (hazard ratio 0.40, $p < 0.05$). The interaction of genotype with β-blockers in the combined LQT1 and LQT2 model (n = 785) suggested insufficient statistical evidence (likelihood ratio test p = 0.14) (data not shown).

UNIVARIATE ANALYSES: RECURRENT CARDIAC EVENTS. Recurrent cardiac events occurred less frequently in patients initially prescribed metoprolol, nadolol, and atenolol compared with propranolol (p = 0.002) (Central Illustration), with the 2-year cumulative probabilities of cardiac events being 27%, 31%, 33%, and 48%, respectively. The 5-year cumulative probability of cardiac events ranged from 33% to 61%.

MULTIVARIATE TIME-DEPENDENT ANALYSES: RECURRENT CARDIAC EVENTS. The hazard ratios for subsequent cardiac events among patients who had a first cardiac event while taking β-blocker therapy (n = 315) indicate that β-blockers are not equivalent (3-df likelihood ratio test p = 0.004) (Table 4). Risk reduction in recurrent cardiac events for metoprolol, nadolol, and atenolol compared with propranolol were 59% (p = 0.04), 48% ($p < 0.01$), and 43% ($p < 0.01$), respectively.

DISCUSSION

This study compares the efficacy of various β-blockers in a large LQTS population with long-term follow-up. In previous studies, we showed that β-blockers are effective in reducing the overall risk of cardiac events in both adults (9) and children (10), and β-blockers are considered first-line therapy for patients with LQTS (11). Controversy exists regarding the most effective β-blocker, and earlier small studies suggested nonuniform effects for different drugs (12). Our study indicates that although different β-blockers are similarly effective in preventing first cardiac events in the general LQTS population, further attention should be given to some agents over the others, particularly in specific LQTS genotypes and in reduction of recurrent events.

TABLE 2 Drug-Specific Cardiac Event Rates on β-Blocker Therapy and Covariate-Adjusted Hazard Ratios Relative to Discontinuing β-Blockers*

Time-Dependent Variable	First Cardiac Events†	Hazard Ratio‡ (95% CI)	p Value	Aborted Cardiac Arrest/Sudden Cardiac Death†	Hazard Ratio‡ (95% CI)	p Value
Atenolol	100/414 (24.2)	0.71 (0.50–1.01)	0.06	18/418 (4.3)	0.38 (0.20–0.74)	0.004
Metoprolol	25/147 (17.0)	0.70 (0.43–1.15)	0.16	1/147 (0.7)	0.08 (0.01–0.62)	0.02
Propranolol	160/395 (40.5)	0.65 (0.46–0.90)	0.01	42/352 (11.9)	0.42 (0.24–0.74)	0.002
Nadolol	61/363 (16.8)	0.51 (0.35–0.74)	<0.001	12/386 (3.1)	0.29 (0.14–0.61)	<0.001
Any β-blocker (pool of all 4 groups)	346/1,319 (26.2)	0.63 (0.47–0.86)	0.004	73/1,303 (5.6)	0.37 (0.22–0.61)	<0.001
Test of equality of 4 drug-specific hazard ratios§			0.19			0.16

Values are n/N (%), unless otherwise noted. *Numbers of patients who discontinued β-blocker therapy at the end of follow-up were 211 for first cardiac events analysis (total events = 49, 23.2%) and 227 for aborted cardiac arrest/sudden death (total events = 20, 8.8%). Total first cardiac events = 395, of which aborted cardiac arrest = 25 and death = 31. †Number of patients in each group at the end of follow-up (n). These are different from baseline counts because the analyses were time dependent, allowing patients to switch and go on and off drugs during follow-up. ‡Adjusted hazard ratios: see the methods section for covariates included in the Cox models when computing hazard ratios. §There was insufficient evidence of differential effects by type of β-blocker for first cardiac event or aborted cardiac arrest/sudden cardiac death (3-df likelihood ratio test p = 0.19 and p = 0.16, respectively).

CI = confidence interval.

The main analysis involved patients who were clinically or genetically diagnosed with LQTS, and the 4 β-blockers showed similar risk reduction when compared with not receiving β-blocker therapy. The age when first β-blocker therapy was prescribed was significantly different among the 4 drugs, with propranolol, the first β-blocker on the market, started at a younger age compared with the other β-blockers. It is known from previous studies that younger patients with LQTS are at higher risk for cardiac events compared with patients who are older (10,13). Therefore, adjustments for age and calendar year when β-blocker therapies were initiated were carried out in this study to correct for these confounding factors. Further adjustment for LQTS severity was achieved by including other relevant covariates in the multivariate Cox-model as described earlier.

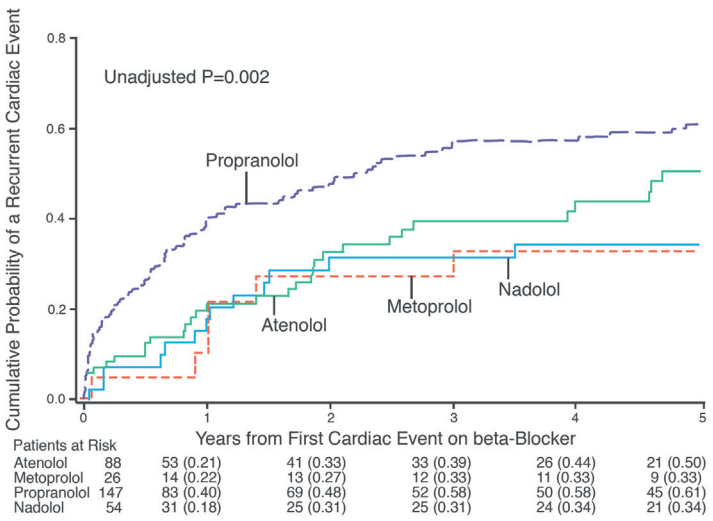
In genotype-specific analysis, all β-blockers were similarly effective in reducing the risk for cardiac events in LQT1 but not in LQT2, despite the *statistically* insufficient evidence of differential efficacy of β-blockers by genotype. However, because the results are close to the 0.1 p value for significance level and there is clinical plausibility to the differences, we report the analyses of the individual genotypes separately. Analysis of β-blockers in LQT2 showed that nadolol provided the only significant risk reduction when compared with other β-blockers. One explanation for differences observed by genotype can be related to triggers that initiate cardiac

TABLE 3 Genotype- and Drug-Specific First Cardiac Event* Rates on β-Blocker Therapy and Covariate-Adjusted Hazard Ratios Relative to Discontinuing β-Blockers† in Patients With LQT1 and LQT2

	LQT1 (n = 379) (Total CE = 87)			LQT2 (n = 406) (Total CE = 85)		
Time-Dependent Variable	First CE‡	Hazard Ratio§ (95% CI)	p Value	First CE‡	Hazard Ratio§ (95% CI)	p Value
Atenolol	21/105 (20.0%)	0.43 (0.22–0.86)	0.02	28/114 (24.6%)	1.04 (0.48–2.27)	0.92
Metoprolol	3/20 (15.0%)	0.44 (0.13–1.54)	0.2	10/46 (21.7%)	0.82 (0.32–2.09)	0.67
Propranolol	26/72 (36.1%)	0.38 (0.19–0.73)	0.004	28/100 (28.0%)	0.65 (0.29–1.42)	0.28
Nadolol	22/125 (17.6%)	0.50 (0.25–0.98)	0.04	10/109 (9.2%)	0.40 (0.16–0.98)	0.04
Test of equality of 4 drug-specific hazard ratios‖¶			0.83			0.04

Values are n/N (%), unless otherwise noted. *CE denotes cardiac events (syncope or aborted cardiac arrest [ACA] or death), total first CE in LQT1 = 87; of which ACA = 3 and death = 4, total first CE in LQT2 = 85; of which ACA = 6 and death = 2. †Numbers of patients who discontinued β-blocker therapy at the end of follow-up were 57 for LQT1 (total events = 15, 26.3%) and 37 for LQT2 (total events = 9, 24.3%). ‡Number of patients at end of follow-up. These numbers are different from baseline counts because the analyses were time dependent, allowing patients to switch and go on and off drugs during follow-up. §Adjusted hazard ratios: see the methods section for covariates included in the Cox models when computing hazard ratios. ‖In patients with LQT2, there was significant evidence of differential effects by type of β-blocker (3-df LRT p = 0.04); in patients with LQT1, there was insufficient evidence (3-df LRT p = 0.83). ¶Test of equality for the interaction of genotype with β-blockers in the combined LQT1 + LQT2 model (n = 785) suggested insufficient statistical evidence (4-df LRT p= 0.14) (data not shown).

CE = cardiac event; CI = confidence interval; LQT1 = long QT syndrome genotype 1; LQT2 = long QT syndrome genotype 2; LRT = likelihood ratio test.



CENTRAL ILLUSTRATION Cumulative Probability of a Subsequent Cardiac Event Among Patients With 1 Cardiac Event While Taking β-Blocker Therapy

Kaplan-Meier estimates of the cumulative probability of a subsequent cardiac event following 1 cardiac event while taking β-blocker therapy, stratified by type of β-blocker: atenolol, metoprolol, nadolol, or propranolol. The p value was based on the 4-group log-rank test, unadjusted for covariates or time-dependent changes to β-blocker status. The numbers of subjects at risk are given yearly, up to 5 years, for a first recurrent cardiac event while taking β-blockers.

events within each genotype. In LQT1, patients are more likely to have cardiac events during exercise, when β-adrenergic activity is meaningfully augmented (14). Any β-blocker that can achieve β-adrenergic blockade is likely to be effective. In fact this is observed in nadolol, which showed nearly a similar risk reduction (hazard ratio) in both LQT1 and LQT2, as a result of its β-adrenergic blocking activity.

In contrast, patients with LQT2 are less likely to experience cardiac events during exercise because their events are triggered by auditory stimulation or sudden startle (15), activities mediated by both neurotransmitters and catecholamines. It could be that nadolol, a hydrophilic long-acting noncardioselective β-blocker with the longest elimination half-life, offers the most stable, lasting degree of β-blockade. Other pharmacodynamic properties, such as a lack of both intrinsic sympathomimetic activity and membrane-stabilizing activity, may also play roles in this beneficial effect observed in LQT2. More studies are necessary to investigate the mechanism behind this observation.

In the recurrent cardiac events analysis, we compared the efficacy of β-blockers in patients who had a prior cardiac event while taking β-blockers. Our results suggested that β-blockers are not all alike in preventing recurrent events, and propranolol seemed to be the least effective of the 4 β-blockers. Clinically, patients who continue to have cardiac events despite taking β-blocker therapy are considered to be a very high-risk group (11,16). This novel observation for propranolol could reflect its different role in this high-risk LQTS population. Kawakami et al. (17) studied the effect of β-blockers on the wild-type hERG channel, and the rapid component of the cardiac potassium channel (IK*r*) was blocked by high concentrations of propranolol. This effect was not seen with atenolol or metoprolol within the therapeutic concentration range. It may be that high-risk patients with LQTS who have recurrent events while taking β-blockers are more sensitive to propranolol's undesirable hERG-blocking action, which may explain why, given the drug's other useful properties such as its antiadrenergic and INa blocking effects (18,19), propranolol is not as effective in these patients as expected. Clinical experience suggests that patients who experience cardiac events while taking β-blockers are at augmented risk for sudden cardiac death, and such patients may benefit from nonpharmacological antiadrenergic therapies such as left cervicothoracic sympathetic denervation or an ICD (11,20,21).

Our findings differ from those from a recent study reported by Chockalingam et al. (5). In their study, the analysis of cardiac events in previously *asymptomatic* patients (n = 281) showed no differences in cardiac event occurrence among metoprolol, propranolol, and nadolol. Although there was a significant age difference when β-blockers were started ($p < 0.001$) in the overall population (5), but not in the subset of previously symptomatic patients ($p = 0.8$), no adjustment for this age difference was performed. In contrast to our study, in which we found 25 cardiac events (17%) and only 1 serious event (0.7%) in patients with LQTS who started on metoprolol, the study by Chockalingam et al. study found a higher rate (29%) of cardiac events among symptomatic patients receiving metoprolol compared with those taking propranolol and nadolol (5). Our study included a 4-fold larger number of patients with LQTS overall (1,530 compared with 382) and of patients taking metoprolol (147 compared with 35). Our observation indicates fewer cardiac events for patients with LQTS who were receiving metoprolol therapy (17%), after adjusting for the history of prior cardiac events (symptomatic patients) in the Cox model. In addition, our time-dependent analyses took into

account the different follow-up times among the patients receiving various β-blocker therapies with adjustment for relevant covariates, as described earlier, several factors that should contribute to more accurate analysis of risk/benefit considerations. It is interesting that Chockalingam et al. (5) found that propranolol shortened the QTc, but this has not generally been our experience with β-blockers (11). We previously showed that nadolol was significantly effective in reducing the risk for cardiac events in LQT2, but propranolol was not (22).

We excluded patients treated with ICDs in our analysis so we could focus exclusively on β-blocker therapy as a pharmacological therapy, as described in the methods section. When patients with ICDs inserted before or during β-blocker therapy were included in the analyses, the results were essentially the same.

STUDY LIMITATIONS. Similar to other studies using data from registries, there are limitations inherent in this type of observational study. Lack of randomization is the most important concern. Randomization of therapy and long-term follow-up of patients with a rare disease (e.g., LQTS) and infrequent events are nearly impossible to do within a reasonable time frame. This observational study adjusted for important confounding factors by using appropriate statistical analyses. We believe that our adjustments for age and year when β-blockers were initiated are important for reducing potential bias in this study. Patients' compliance in taking their medications is another issue (23). This Registry study contains reliable data on the starting and stopping of β-blockers in the time-dependent analyses, and we believe such information provides reasonably reliable information about patients' compliance with β-blocker therapy. In addition, we believe that whatever unmeasured noncompliance exists would likely be similar among patients taking the various β-blockers. Therefore, noncompliance, if present, should not differentially affect the adjusted hazard ratios reported in the analysis.

Although we do not have consistent information of β-blocker dosage by weight over time for all patients (on and off), we calculated the doses for both adults and younger patients in milligrams per day and also in milligrams per kilogram for those for whom weight was available at the initiation of their known dose of β-blocker therapy, as shown in **Table 1**. Both quantifications of β-blocker therapy doses appear reasonable and within the accepted and recommended dosing for this therapy in LQTS.

TABLE 4 Drug-Specific Recurrent Cardiac Event Rates* and Covariate-Adjusted Hazard Ratios Relative to Propranolol† Among Patients With 1 Prior Cardiac Event on β-Blockers

Time-Dependent Variable	Number of Patients at End of Follow-Up‡	Recurrent Cardiac Events§	Hazard Ratio‖ (95% CI)	p Value
Atenolol: propranolol	87	33 (37.9)	0.57 (0.38–0.87)	0.009
Metoprolol: propranolol	23	6 (26.1)	0.41 (0.17–0.98)	0.04
Nadolol: propranolol	65	22 (33.9)	0.52 (0.32–0.84)	0.008
No β-blockers (off therapy during follow-up)	25	10 (40.0)	0.91 (0.46–1.80)	0.77
Test of equality of 4 drug-specific hazard ratios¶				0.004

Values are n (%), unless otherwise noted. *The time origin for this analysis was the date of the first cardiac event while taking β-blockers. †Number of patients who were on propranolol at the end of follow-up was 115 (recurrent events = 83, 72.2%). ‡Number of patients at end of follow-up who already had 1 prior first cardiac event on β-blockers. §Cardiac events include syncope, aborted cardiac arrest (ACA), or death at the end of follow-up. Total recurrent cardiac events = 154, of which ACA = 8 and death = 7. ‖Adjusted hazard ratios: see the methods section for covariates included in the Cox models when computing hazard ratios. ¶There was evidence of differential effects by type of β-blocker for recurrent events (3-df likelihood ratio test p = 0.004) when comparing hazard ratios for atenolol, metoprolol, nadolol, and propranolol, with propranolol as the least effective.

CI = confidence interval.

CONCLUSIONS

In conclusion, the 4 major β-blockers seem to be equally effective in reducing the risk of first cardiac events in LQTS. Our findings highlight the somewhat augmented therapeutic benefit of nadolol, and we believe it is the preferred β-blocker in the general management of patients with LQTS, with slightly better effect in patients with LQT2 compared with other β-blockers. Patients experiencing cardiac events while receiving β-blocker therapy are at high risk for subsequent life-threatening cardiac events, and our findings indicate that propranolol is the least effective agent in preventing recurrent cardiac events in these high-risk patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Beta-blockers differ in selectivity for adrenergic receptor subtypes, adverse effects, and dosing, and these may influence efficacy and tolerability in patients with genetic subtypes of the LQTS.

TRANSLATIONAL OUTLOOK: Further studies are needed to guide genotype-specific selection of optimum β-blockers agents for use in selected subpopulations of patients with LQTSs.

REFERENCES

1. Goldenberg I, Zareba W, Moss AJ. Long QT syndrome. Curr Probl Cardiol 2008;33:629–94.

2. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol 2006;48:e247–346.

3. Antonelli-Incalzi R, Pedone C. Respiratory effects of beta-adrenergic receptor blockers. Curr Med Chem 2007;14:1121–8.

4. Lewis RV, Lofthouse C. Adverse reactions with beta-adrenoceptor blocking drugs: an update. Drug Saf 1993;9:272–9.

5. Chockalingam P, Crotti L, Girardengo G, et al. Not all beta-blockers are equal in the management of long QT syndrome types 1 and 2: higher recurrence of events under metoprolol. J Am Coll Cardiol 2012;60:2092–9.

6. Moss AJ, Robinson JL. Long QT syndrome. Heart Dis Stroke 1992;1:309–14.

7. Lehnart SE, Ackerman MJ, Benson DW Jr., et al. Inherited arrhythmias: a National Heart, Lung, and Blood Institute and Office of Rare Diseases workshop consensus report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affecting ion channel function. Circulation 2007;116:2325–45.

8. Cox D. Regression models and life tables (with discussion). J R Stat Soc Series B Stat Methodol 1972;34:187–220.

9. Sauer AJ, Moss AJ, McNitt S, et al. Long QT syndrome in adults. J Am Coll Cardiol 2007;49:329–37.

10. Goldenberg I, Moss AJ, Peterson DR, et al. Risk factors for aborted cardiac arrest and sudden cardiac death in children with the congenital long-QT syndrome. Circulation 2008;117:2184–91.

11. Moss AJ, Zareba W, Hall WJ, et al. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. Circulation 2000;101:616–23.

12. Chatrath R, Bell CM, Ackerman MJ. Beta-blocker therapy failures in symptomatic probands with genotyped long-QT syndrome. Pediatr Cardiol 2004;25:459–65.

13. Locati EH, Zareba W, Moss AJ, et al. Age- and sex-related differences in clinical manifestations in patients with congenital long-QT syndrome: findings from the International LQTS Registry. Circulation 1998;97:2237–44.

14. Schwartz PJ, Priori SG, Spazzolini C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation 2001;103:89–95.

15. Wilde AA, Jongbloed RJ, Doevendans PA, et al. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS2) patients from KVLQT1-related patients (LQTS1). J Am Coll Cardiol 1999;33:327–32.

16. Priori SG, Napolitano C, Schwartz PJ, et al. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. JAMA 2004;292:1341–4.

17. Kawakami K, Nagatomo T, Abe H, et al. Comparison of HERG channel blocking effects of various beta-blockers: implication for clinical strategy. Br J Pharmacol 2006;147:642–52.

18. Wang DW, Mistry AM, Kahlig KM, et al. Propranolol blocks cardiac and neuronal voltage-gated sodium channels. Front Pharmacol 2010;1:144.

19. Besana A, Wang DW, George AL Jr., et al. Nadolol block of Nav1.5 does not explain its efficacy in the long QT syndrome. J Cardiovasc Pharmacol 2012;59:249–53.

20. Schwartz PJ, Priori SG, Cerrone M, et al. Left cardiac sympathetic denervation in the management of high-risk patients affected by the long-QT syndrome. Circulation 2004;109:1826–33.

21. Zareba W, Moss AJ, Daubert JP, et al. Implantable cardioverter defibrillator in high-risk long QT syndrome patients. J Cardiovasc Electrophysiol 2003;14:337–41.

22. Goldenberg I, Bradley J, Moss A, et al. Beta-blocker efficacy in high-risk patients with the congenital long-QT syndrome types 1 and 2: implications for patient management. J Cardiovasc Electrophysiol 2010;21:893–901.

23. Vincent GM, Schwartz PJ, Denjoy I, et al. High efficacy of beta-blockers in long-QT syndrome type 1: contribution of noncompliance and QT-prolonging drugs to the occurrence of beta-blocker treatment "failures." Circulation 2009;119:215–21.

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