Not All Beta-Blockers Are Equal in the Management of Long QT Syndrome Types 1 and 2

Higher Recurrence of Events Under Metoprolol

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Objectives   The purpose of this study was to compare the efficacy of beta-blockers in congenital long QT syndrome (LQTS).

Background   Beta-blockers are the mainstay in managing LQTS. Studies comparing the efficacy of commonly used beta-blockers are lacking, and clinicians generally assume they are equally effective.

Methods   Electrocardiographic and clinical parameters of 382 LQT1/LQT2 patients initiated on propranolol (n = 134), metoprolol (n = 147), and nadolol (n = 101) were analyzed, excluding patients <1 year of age at beta-blocker initiation. Symptoms before therapy and the first breakthrough cardiac events (BCEs) were documented.

Results   Patients (56% female, 27% symptomatic, heart rate 76 ± 16 beats/min, QTc 472 ± 46 ms) were started on beta-blocker therapy at a median age of 14 years (interquartile range: 8 to 32 years). The QTc shortening with propranolol was significantly greater than with other beta-blockers in the total cohort and in the subset with QTc >480 ms. None of the asymptomatic patients had BCEs. Among symptomatic patients (n = 101), 15 had BCEs (all syncopes). The QTc shortening was significantly less pronounced among patients with BCEs. There was a greater risk of BCEs for symptomatic patients initiated on metoprolol compared to users of the other 2 beta-blockers combined, after adjustment for genotype (odds ratio: 3.95, 95% confidence interval: 1.2 to 13.1, p = 0.025). Kaplan-Meier analysis showed a significantly lower event-free survival for symptomatic patients receiving metoprolol compared to propranolol/nadolol.

Conclusions   Propranolol has a significantly better QTc shortening effect compared to metoprolol and nadolol, especially in patients with prolonged QTc. Propranolol and nadolol are equally effective, whereas symptomatic patients started on metoprolol are at a significantly higher risk for BCEs. Metoprolol should not be used for symptomatic LQT1 and LQT2 patients.   (J Am Coll Cardiol 2012;60:2092–9) © 2012 by the American College of Cardiology Foundation

Congenital long QT syndrome (LQTS) is a primary inherited arrhythmia syndrome associated with an increased propensity to arrhythmogenic syncope and sudden death. Abnormal cardiac repolarization evident as prolonged QT interval on the electrocardiogram (ECG) is the signature feature of LQTS. Since the 1970s, beta-blockers have been the mainstay in managing this disorder primarily because the trigger for most life-threatening arrhythmias is a sudden increase in sympathetic activity, especially in LQT1 and LQT2 patients (1,2).

See page 2100

The efficacy of beta-blockers in reducing LQTS-associated cardiac events is established (3,4). Propranolol, the prototypic beta-blocking agent, has been studied most extensively and has been shown to either decrease or prevent an increase in transmural dispersion of repolarization in response to strong sympathetic stimulation, a mechanism contributing to its antiarrhythmic effect (5). Although several studies have clearly demonstrated a very favorable response to beta-blockers in symptomatic LQTS patients, it is also evident that 20% to 30% of previously symptomatic patients experience a breakthrough cardiac event (BCE) while receiving beta-blocker therapy (6−8). Concern that not all beta-blockers provide equivalent protection in LQTS and that this could contribute to treatment failure has been expressed in the past (9,10). However, actual comparisons between different beta-blockers are lacking. Recent findings concerning the differential mechanism of action of propranolol and metoprolol on the cardiac sodium (Na^+) channel have thrown light on the probable physiology underlying this significant therapeutic aspect (11). The purpose of this study was to compare the efficacy of commonly used beta-blockers in LQTS by comparing the baseline and on-therapy clinical and electrocardiographic characteristics of patients treated with different beta-blockers and by correlating this with the occurrence of BCEs on follow-up.

Methods

Study population. LQTS patients, both index patients and family members, managed at the participating university hospitals were included if they had a genetically confirmed LQT1 or LQT2 mutation, were initiated on therapy with beta-blockers, and had at least 1 pre-therapy (baseline) and 1 on-therapy ECG for review. Patients diagnosed with LQTS and initiated on beta-blocker therapy in their first year of life were not included in the study. Patients with LQT3-13 or multiple mutations were not included. Patients lost to follow-up after initial evaluation (n = 9) and patients with history of QTc-prolonging drug intake at the time of baseline evaluation (n = 3) were excluded from the study. A total of 382 patients started on therapy with propranolol (n = 134), metoprolol (n = 147), and nadolol (n = 101) were included. We did not include patients treated with other beta-blockers because of small patient numbers, which might have led to incorrect inferences.

Data collection and management. Demographic data and details of personal and family history were obtained for all patients. Syncope (defined as transient loss of consciousness that was abrupt in onset and offset), near drowning, seizure episodes with associated loss of consciousness, and aborted cardiac arrest (ACA, requiring external defibrillation as part of resuscitation) were considered pertinent LQTS-related symptoms. The last ECG before initiation of beta-blockers (baseline) and the first available ECG after initiation of therapy (on-therapy) were retrieved for analysis, and the time interval between the 2 was documented.

The ECG analyses were performed by experienced physicians blinded to therapy details. The QT interval was measured manually from the beginning of the QRS complex to the end of the T-wave in lead II or V_5. The end of the T-wave was determined as the intersection point between the isoelectric baseline and the tangent representing the maximal downward slope of the positive T-wave or maximal upward slope of the negative T-wave. The mean of 3 consecutive QT intervals was used. Corrected QT interval (QTc) was obtained using Bazett's formula. For purposes of this study, QTc was considered normal if ≤450 ms, borderline if 451 to 480 ms, and prolonged if >480 ms.

Follow-up data on beta-blockers included the initiation date, date of switch to another beta-blocker (considering first switch if switched more than once), date of beta-blocker discontinuation (if applicable), and details of BCEs if any. A BCE was defined as syncope, ACA, appropriate implantable cardioverter defibrillator (ICD) shock, or sudden cardiac death occurring while receiving beta-blockers, taking into account the first BCE for subjects with multiple BCEs. Beta-blocker compliance and the nonusage of other QT-prolonging drugs at the time of the BCEs had been

verified by the caring physicians. Any BCEs occurring at a time of admitted noncompliance were not included. Details of ancillary LQTS therapy with ICD, pacemaker, and/or surgical left cardiac sympathetic denervation (LCSD) were documented.

Statistical analysis. Continuous variables are presented as mean ± SD and analyzed by *t* test for independent or paired samples, as appropriate, and by 1-way analysis of variance, according to the number of groups compared, with Bonferroni correction for multiple comparisons. Whenever the distribution was skewed, continuous variables, presented as median and interquartile range (IQR), were compared by Mann-Whitney and Kruskal-Wallis tests. Categorical variables are presented as number of patients (n) and/or percentage (%) and analyzed by the chi-square test. Adjusted odds ratio with 95% confidence interval was estimated from a multivariate logistic regression model used to determine the association between beta-blockers and occurrence of BCEs in previously symptomatic patients, while controlling for genotype. Kaplan-Meier analysis, with log-rank test for comparisons, was used to estimate the cumulative event-free survival of symptomatic patients, taking the first BCE as the endpoint. However, if beta-blocker switch occurred before BCE, censoring was done at the time of switch. In patients without a BCE, censoring was done at the time of beta-blocker switch or at the time of beta-blocker discontinuation or at the time of the study, whichever came first. All analyses were performed using SPSS version 18.0 (SPSS, Inc., Chicago, Illinois), and $p < 0.05$ was considered statistically significant.

Results

Clinical characteristics of the study subjects (n = 382) started on the different beta-blockers are provided in Table 1.

Females constituted 56% of the study population. Symptoms before treatment were present in 27% of the subjects, with syncope being the most common symptom. There were more LQT1 patients (54%) than LQT2 patients (46%) in the total cohort. The distribution of sex, genotype, and symptomatic patients was different among the beta-blocker groups. The baseline heart rate of the study population was 76 ± 16 beats/min and was comparable among the beta-blocker groups; the baseline QTc was 472 ± 46 ms and was different among the beta-blocker groups. Median age at beta-blocker initiation was 14 years (IQR: 8 to 32 years) in the total cohort, and differed among the 3 groups. The on-therapy heart rate and QTc were different compared to the baseline heart rate and QTc within each beta-blocker group ($p < 0.001$ for all paired comparisons). However, while the change in heart rate with beta-blocker initiation was comparable among the groups ($p = 0.9$), the change in QTc with propranolol was greater than that with metoprolol ($p = 0.003$) and with nadolol ($p = 0.004$). Median initial beta-blocker dosages documented at the time of on-therapy ECG were propranolol, 1.8 mg/kg daily (IQR: 1.2 to 2 mg/kg daily); metoprolol, 0.9 mg/kg daily (IQR: 0.7 to 1.6 mg/kg daily); and nadolol, 0.9 mg/kg daily (IQR: 0.7 to 1.2 mg/kg daily). Regular propranolol was used by 99% of propranolol users and sustained-release metoprolol by 90% of metoprolol users.

QTc shortening on the basis of baseline QTc. Given the longer baseline QTc in the propranolol group compared to the other groups, and the appearance of dependence of QTc shortening on the baseline QTc, all subjects were further subdivided on the basis of whether the baseline QTc was normal (≤450 ms), borderline (451 to 480 ms) or prolonged (>480 ms) (Fig. 1). The baseline heart rate differed among beta-blocker groups within the normal QTc subset, and the

Table 1	Clinical Characteristics of Patients on Basis of Initial Beta-Blocker				
Characteristics	**Total (n = 382)**	**Propranolol (n = 134)**	**Metoprolol (n = 147)**	**Nadolol (n = 101)**	**p Value**
Female	215 (56)	65 (49)	94 (64)	56 (55)	0.03
Symptoms before therapy					
Syncope	90 (24)	46 (34)	30 (20)	14 (14)	0.001
ACA	11 (3)	5 (4)	5 (3)	1 (1)	0.4
Genotype					<0.001
LQT1	207 (54)	79 (59)	59 (40)	69 (68)	
LQT2	175 (46)	55 (41)	88 (60)	32 (32)	
Baseline HR, beats/min	76 ± 16	78 ± 18	75 ± 15	74 ± 13	0.06
Baseline QTc, ms	472 ± 46	480 ± 47*	469 ± 49	465 ± 40	0.03
Median age at start of BB, yrs	14 (8–32)	10 (6–22)	21 (11–38)	14 (9–30)	<0.001
On-therapy HR, beats/min	64 ± 14	67 ± 16	64 ± 12	62 ± 13	0.05
On-therapy QTc, ms	454 ± 39	453 ± 37	456 ± 44	452 ± 34	0.8
Median TI, months	8 (4–13)	8 (3–13)	6 (3–13)	12 (8–14)	<0.001
ΔHR, beats/min	11 ± 12	12 ± 12	11 ± 12	11 ± 12	0.9
ΔQTc, ms	18 ± 34	27 ± 38†	14 ± 34	12 ± 28	0.001

Values are n (%), mean ± SD, or median (interquartile range). *p < 0.05 versus nadolol; †p < 0.01 versus metoprolol and versus nadolol.
ACA = aborted cardiac arrest; BB = beta-blocker; HR = heart rate; TI = time interval between baseline and on-therapy electrocardiograms; Δ = change in electrocardiography parameter with beta-blocker initiation.
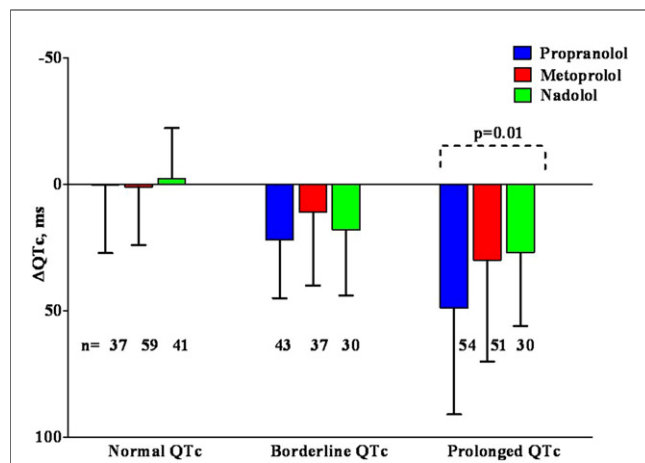
Figure 1   **Effect of Baseline QTc on QTc Shortening**

Baseline QTc was taken as normal if ≤450 ms, borderline if 451 ms to 480 ms, and prolonged if >480 ms. The Δ indicates change in electrocardiography parameter with beta-blocker initiation. **Blue bars** indicate propranolol; **red bars** indicate metoprolol; **green bars** indicate nadolol.

Figure 2   **Progression of QTc With Initiation of Propranolol and Switch to Metoprolol**

Progression of QTc (mean ± SD) with initiation of propranolol and subsequent switch to metoprolol in a subset of 14 patients. "Baseline" indicates QTc immediately before initiation of propranolol therapy; "propranolol" indicates first QTc measurement on propranolol; "prior to switch" indicates QTc on propranolol before switch; "at switch" indicates QTc on propranolol at the time the decision to switch was made; "metoprolol" indicates QTc on metoprolol after switch; and "TI" is time interval in months.

age at therapy initiation differed within the normal and prolonged QTc subsets. Now, the baseline QTc was expectedly comparable within all 3 QTc subsets. The QTc shortening with propranolol, metoprolol, and nadolol in the normal QTc subset (0 ± 27 ms, 1 ± 23 ms, −2 ± 20 ms; p = 0.8) and in the borderline QTc subset (22 ± 23 ms, 11 ± 29 ms, 18 ± 26 ms; p = 0.2) were comparable but was significantly different in the prolonged QTc subset (49 ± 42 ms, 30 ± 40 ms, 27 ± 29 ms; p = 0.01). Bonferroni test showed the QTc shortening with propranolol to be different from that with metoprolol (p = 0.04) and with nadolol (p = 0.04) in the prolonged QTc subset.

Progression of QTc in subjects switched from propranolol to metoprolol. A subset of patients (n = 14, from 2 participating centers) initiated on propranolol and switched to metoprolol during follow-up were retrospectively analyzed to study QTc progression (Fig. 2). In this subset, there were 11 LQT1 patients and 3 LQT2 patients. Median age at start of propranolol was 6 years (IQR: 6 to 7 years), and median age at switch to metoprolol was 11 years (IQR: 9 to 13 years). On-therapy QTc (447 ± 20 ms) with propranolol measured at a median time of 7 months (IQR: 5 to 10 months) after initiation differed significantly from the baseline QTc (465 ± 29 ms, p = 0.005). The QTc on metoprolol (464 ± 39 ms) measured at a median time of 12 months (IQR: 6 to 18 months) after the switch was significantly longer than the QTc on propranolol (445 ± 28 ms) measured at a median time of 18 months (IQR: 12 to 18 months) before the switch (p = 0.004).

Comparison of LQT1 and LQT2 subjects. A similar proportion of LQT1 and LQT2 subjects were symptomatic before therapy (Table 2). While baseline heart rate was comparable between the genotypes, LQT2 subjects had a longer baseline QTc (p = 0.01) than LQT1 subjects. Age at

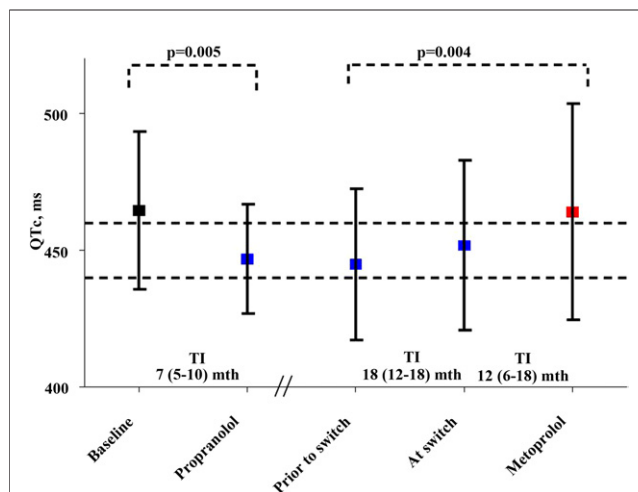beta-blocker initiation was greater (p = 0.04) in LQT2 subjects. Overall QTc shortening and that due to initiation of propranolol, metoprolol, and nadolol were comparable between the genotypes.

Analysis of occurrence of BCEs on the basis of symptoms before treatment. Among asymptomatic subjects (n = 281), 30% were initiated on propranolol, 40% on metoprolol, and 30% on nadolol. There were no BCEs documented during a median follow-up period of 6 years (IQR: 2 to 10 years) on propranolol, 6 years (IQR: 3 to 9 years) on metoprolol, and 4 years (IQR: 3 to 6 years) on nadolol.

The clinical characteristics of previously symptomatic (n = 101) subjects initiated on the 3 beta-blockers are shown in Table 3. Sex, genotype, and age at beta-blocker initiation were comparable among the subjects in the 3

Table 2   **Clinical Characteristics of Patients on the Basis of Genotype**

Characteristics	LQT1 (n = 207)	LQT2 (n = 175)	p Value
Symptoms before therapy	56 (27)	45 (26)	0.8
Baseline HR, beats/min	77 ± 15	74 ± 16	0.08
Baseline QTc, ms	467 ± 42	478 ± 50	0.01
Median age at start of BB, yrs	12 (7–30)	18 (10–34)	0.04
ΔHR, beats/min	11 ± 12	11 ± 12	0.9
ΔQTc, ms	18 ± 32	18 ± 37	0.9
ΔQTc with propranolol, ms	25 ± 35	29 ± 43	0.6
ΔQTc with metoprolol, ms	16 ± 29	12 ± 37	0.5
ΔQTc with nadolol, ms	11 ± 30	14 ± 22	0.6

Values are n (%), mean ± SD, or median (interquartile range).
Abbreviations as in Table 1.

Table 3	Clinical Characteristics of Symptomatic Patients on the Basis of Initial Beta-Blocker				
Characteristics	Total (n = 101)	Propranolol (n = 51)	Metoprolol (n = 35)	Nadolol (n = 15)	p Value
Female	73 (72)	36 (71)	26 (74)	11 (73)	0.9
LQT1	56 (55)	32 (62)	14 (41)	10 (67)	0.07
Baseline HR, beats/min	74 ± 14	74 ± 14	75 ± 14	69 ± 11	0.3
Baseline QTc, ms	499 ± 51	502 ± 52	497 ± 48	493 ± 54	0.8
Median age at start of BB, yrs	22 (10–34)	18 (8–34)	25 (17–38)	22 (9–32)	0.2
On-therapy HR, beats/min	62 ± 12	63 ± 14	61 ± 9	60 ± 13	0.7
On-therapy QTc, ms	474 ± 41	469 ± 40	478 ± 44	478 ± 35	0.5
Median TI, months	6 (3–17)	8 (3–16)	5 (2–17)	8 (3–20)	0.7
ΔHR, beats/min	12 ± 12	11 ± 12	14 ± 12	9 ± 9	0.3
ΔQTc, ms	26 ± 37	33 ± 39	19 ± 37	15 ± 28	0.1
BCE	15 (15)	4 (8)	10 (29)	1 (7)	0.02

Values are n (%), mean ± SD, or median (interquartile range).
BCE = breakthrough cardiac event; other abbreviations as in Table 1.

beta-blocker groups in this cohort of patients with symptoms before treatment. With baseline and on-therapy ECG parameters being comparable, there was an overall significant difference (p = 0.018) in the occurrence of BCEs among the 3 beta-blocker groups (Fig. 3). All 15 BCEs were syncopes. Median beta-blocker dosages documented at the time of BCEs were propranolol, 2.5 mg/kg daily (IQR: 1.3 to 3 mg/kg daily), and metoprolol, 1.4 mg/kg daily (IQR: 0.9 to 2.5 mg/kg daily). The only patient who had a BCE while on nadolol therapy was receiving a dose of 0.8 mg/kg daily. The BCEs were more frequent among patients using regular metoprolol at a twice-daily dosing than among patients using sustained-release metoprolol at once-a-day dosing (18% vs. 5%, p = 0.04). There was only 1 sudden cardiac death, which, however, did not occur as a first BCE: a previously symptomatic LQT1 male patient initiated on propranolol at the age of 5 years was switched to metoprolol at the age of 8 years. He experienced a syncope (first BCE) at the age of 11 years while playing football and died a few

months later of an out-of-hospital cardiac arrest (second BCE) while swimming, still under therapy with metoprolol.

As expected, the use of an ICD (18% vs. 0.4%, p < 0.001), pacemaker (3% vs. 0.7%, p = 0.09), and LCSD (7% vs. 0%, p < 0.001) differed between symptomatic and asymptomatic subjects.

Comparison of symptomatic subjects with and without BCE. Sex, baseline heart rate, baseline QTc, and age at therapy initiation were comparable between symptomatic patients with or without BCEs (Table 4). However, symptomatic LQT2 patients had more BCEs compared to symptomatic LQT1 patients (p = 0.02). Also, patients with BCEs had lesser QTc shortening (p = 0.02) than patients without BCEs. Median follow-up time on the initial beta-blocker among symptomatic subjects was 2 years (IQR: 1 to 6 years) for propranolol, 4 years (IQR: 2 to 8 years) for metoprolol, and 3 years (IQR: 2 to 5 years) for nadolol (p = 0.4).

Figure 3 shows that the occurrence of BCEs was significantly different according to the initial beta-blocker used. Indeed, while the proportion of BCEs was almost identical (p = 0.9) for symptomatic patients initiated on propranolol
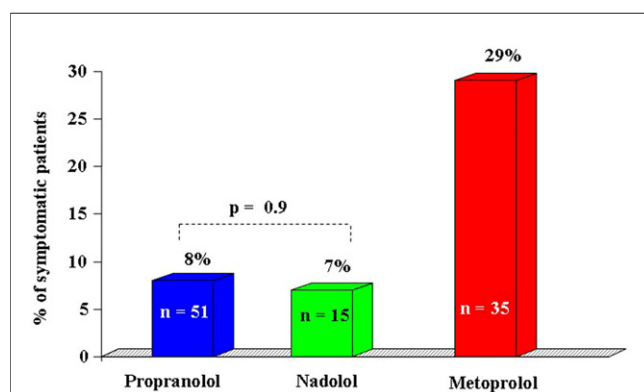
Figure 3   **Occurrence of BCEs in Patients With Symptoms Before Therapy**

Breakthrough cardiac events (BCEs) occurred in 8% of patients receiving propranolol, 7% of patients receiving nadolol, and 29% of patients receiving metoprolol.

Table 4	Comparison of Symptomatic Patients on the Basis of Occurrence of BCE on Initial Beta-Blocker		
	BCE on initial BB		
Variable	Yes (n = 15)	No (n = 86)	p Value
Female	11 (73)	62 (72)	0.9
Genotype			0.02
LQT1	4 (27)	52 (60)	
LQT2	11 (73)	34 (40)	
Baseline HR, beats/min	72 ± 11	74 ± 14	0.6
Baseline QTc, ms	488 ± 42	501 ± 52	0.3
Median age at start of BB, yrs	17 (14–26)	22 (10–34)	0.8
ΔHR, beats/min	12 ± 12	12 ± 11	0.9
ΔQTc, ms	4 ± 24	30 ± 38	0.02

Values are n (%), mean ± SD, or median (interquartile range).
Abbreviations as in Tables 1 and 3.

(8%) and nadolol (7%), it strikingly increased to 29% for patients initiated on metoprolol. That corresponded to a substantially greater risk of suffering a BCE for symptomatic patients initiated on metoprolol compared to patients started on either of the other 2 beta-blockers combined (odds ratio: 3.95, 95% confidence interval: 1.2 to 13.1, p = 0.025), after adjusting for genotype. Consequently, the Kaplan-Meier analysis plotting symptomatic patients initiated on metoprolol (n = 35) against those initiated on propranolol and nadolol combined (n = 66) showed a significant difference (p = 0.02) in the cumulative event-free survival of the patients (Fig. 4). Indeed, by 10 years on beta-blocker therapy, the cumulative event-free survival for propranolol/nadolol users was 91% compared to 60% for metoprolol users.

Discussion

Contrary to the currently prevailing views, in the management of LQTS, not all beta-blockers are equal. The main finding of the present study is that symptomatic patients treated with metoprolol are 4 times more likely to have BCEs than those treated with propranolol and nadolol. This finding will unavoidably impact the clinical management of LQTS. The other major finding of this study is the evidence for a correlation between the antiarrhythmic efficacy of beta-blockers and their ability to shorten the QT interval.

LQTS, beta-blockers, Na$^+$ channel block, and QTc shortening. LQTS is a genotypically and phenotypically heterogeneous disease. The mortality rate among untreated

| Figure 4 | **Kaplan-Meier Estimates of Event-Free Survival of Symptomatic Patients Initiated on Different Beta-Blockers** |

The cumulative event-free survival of symptomatic patients initiated on metoprolol (n = 35) **(red line)** was significantly different (p = 0.02) from that of patients initiated on propranolol and nadolol combined (n = 66) **(green line)**.

symptomatic LQTS patients was as high as 60% to 65% when the first assessment of the beneficial effect of beta-blockers in a large group of patients was made in 1975 (1). Since then, beta-blockers, the mainstay of therapy in LQTS, have been highly effective in reducing mortality (4,10). Whereas propranolol and nadolol are nonselective beta-blockers, metoprolol is relatively beta-1 cardioselective. The largest experience with beta-blockers in LQTS has been that with propranolol. Its main advantages are the good tolerability and the lipophilia that allows it to cross the blood brain barrier, while the need for multiple daily dosing due to its rapid metabolization is the prime disadvantage. Although long-acting, sustained-release preparations of propranolol exist, they are not available in a form suitable for use in children. To overcome the inconvenient dosing schedule with propranolol, an increasing number of patients have been treated with longer-acting beta-blockers such as nadolol and sustained-release metoprolol. Ancillary LQTS therapy in the form of ICD, pacemaker, and/or LCSD is reserved for patients with symptoms despite beta-blockers and for high-risk patients (12). Additionally, when nonselective beta-blockers are contraindicated, for example, for asthma patients, LCSD has been performed with excellent results (unpublished data).

In some of the participating centers, it is common practice to initiate treatment with propranolol or nadolol (on the basis of availability) in young children mainly because of their proven safety for this age group of patients. Propranolol users are quite often switched to another beta-blocker during adolescence to optimize compliance. Similarly, sustained-release metoprolol is used as the initial beta-blocker in adults mainly because of its dosing convenience. These policies explain to some extent the lesser age at therapy initiation for propranolol and nadolol compared to metoprolol. We consider the difference in baseline QTc to have been an effect of these age-based choices rather than being an underlying reason for therapeutic decision making.

Initial concern that all beta-blockers are not equally protective in LQTS, and therefore should not be viewed as equivalent choices, was raised by Chatrath et al. (9), but the small size of that study has limited its impact. The current practice is that physicians typically choose a beta-blocker on the basis of personal experience and then make appropriate changes on the basis of side effects and dosing preferences.

Both beta-adrenoceptor blocking properties and non beta-adrenoceptor mediated actions of propranolol have been proposed to contribute to the antiarrhythmic actions of propranolol (13). Although the Na$^+$ channel blocking efficacy of propranolol has been known for long, a recent study has demonstrated that its blocking effect is particularly more on the late noninactivating Na$^+$ current than on the peak Na$^+$ current, an effect not seen with metoprolol (11). There were no data available on nadolol earlier, but, quite recently, it has been found that nadolol has an ~20% non use-dependent blocking effect on peak Na$^+$ current, and no effect on the late current, whereas metoprolol has no effect
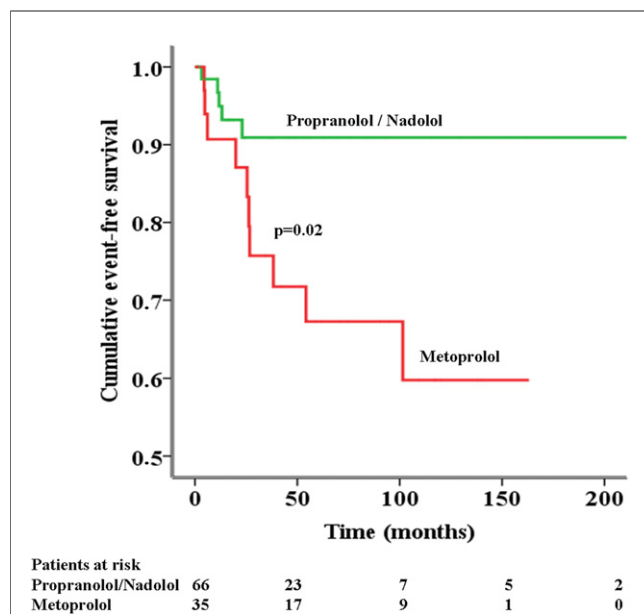
on either the peak or late current (14). Analysis of the biophysical properties of the channel revealed that both nadolol and propranolol cause hyperpolarizing shifts on voltage dependence of activation and steady-state inactivation, whereas metoprolol shifts only the activation curve. These biophysical data clearly explain the differences between propranolol and metoprolol, and provide a partial explanation for the difference between nadolol and metoprolol. Also, the mechanism of the similar clinical efficacy of nadolol and propranolol is not fully understood.

It is clear that in addition to the membrane stabilizing effect of propranolol and nadolol brought about by peak Na^+ current blockade, propranolol has a pronounced late noninactivating Na^+ current blocking ability, which contributes directly to shortening of the action potential duration, and thereby the QTc. The association between QTc shortening and reduction in cardiac events has been shown in earlier studies (4) and is confirmed by the present study. Though beta-blockers do not seem to act on the cardiac potassium channels that are dysfunctional in LQT1 and LQT2, their properties are likely to contribute to a major extent to the drastic reduction in cardiac events in LQT1 and LQT2 patients. The clinical implication of these findings is that prolonged cardiac repolarization in LQTS is shortened more effectively by propranolol than by metoprolol, as the present study confirms. Indeed, by comparing all patients on the basis of their initial beta-blocker, we observed that propranolol had a significantly better QTc-shortening effect compared to metoprolol and nadolol. Furthermore, by grouping subjects on the basis of baseline QTc, the differences in baseline parameters were reduced, and we were able to make comparisons in more homogenous patient subgroups. The pronounced QTc-shortening effect of propranolol in comparison to that of metoprolol and nadolol in subjects with QTc >480 ms can be explained by the net late Na^+ inward current being largest when the action potential duration is longer.

LQTS and efficacy of beta-blockers. Sex, QTc, and the locus of causative mutation have all been identified as factors influencing the clinical course of LQTS patients (2,15). In the present study, the type of LQTS (LQT1 or LQT2) did not influence the occurrence of symptoms before treatment nor did it affect the QTc shortening with beta-blocker initiation. The occurrence of BCEs was significantly influenced by the occurrence of cardiac symptoms before therapy, confirming previous observations (16). Although there were no BCEs among asymptomatic patients, 15% of symptomatic patients had BCEs while still on the initial beta-blocker. The LQT2 genotype and modest QTc shortening with beta-blockers were risk factors for BCEs in this group of patients. Goldenberg et al. (17) have shown that male patients with LQT1 in the <14 years of age group and female patients with LQT2 in the 15 to 40 years age group are at a high risk for cardiac events and that the risk reduction with beta-blockers is significantly high in both groups of patients. The present study, performed with this

cross-over phenomenon in mind, has analyzed the occurrence of BCEs only in the previously symptomatic patients with comparable baseline characteristics. The clinically important finding of our study is that the incidence of first BCEs was rather low, did not include lethal events, and was almost identical among patients receiving propranolol (8%) and nadolol (7%), whereas it was unacceptably high (29%) among those treated with metoprolol. Given the evidence that patients with syncope during beta-blocker therapy are those at a truly high risk of life-threatening events (18), this finding carries significant clinical implications in the management of young symptomatic LQTS patients.

Study limitations. Although this is the largest multicenter study to date comparing the efficacy of commonly used beta-blockers in LQTS, it has the inherent limitation of a retrospective study, namely, lack of homogeneity among patients treated with different beta-blockers. However, grouping patients on the basis of their baseline QTc enabled comparison of the QTc shortening produced by beta-blockers in more homogeneous subgroups of patients. Further, among previously symptomatic patients, where baseline parameters such as sex, genotype, heart rate, QTc, and age at therapy initiation were all comparable, we were able to compare the BCE incidence, which was found to be significantly more among patients initiated on 1 of the beta-blockers. The multivariate logistic regression analysis allowed confirmation of the higher risk of BCEs among metoprolol users even after adjusting for genotype. However, the relatively small number of patients with BCEs and the possibility of residual confounding are recognized as limitations of this study.

Conclusions

This multicenter study on LQTS patients receiving beta-blocker therapy has shown for the first time that propranolol and nadolol are significantly more effective than metoprolol in preventing BCEs in symptomatic patients. Also, propranolol was superior to both nadolol and metoprolol in terms of shortening the cardiac repolarization time, particularly in high-risk patients with markedly prolonged QTc. Symptomatic patients with BCEs had significantly less QTc shortening than the event-free patients. As we have documented an increased risk for symptomatic patients to suffer BCEs with metoprolol, we recommend treatment of symptomatic LQT1 and LQT2 patients with either propranolol or nadolol, as clearly not all beta-blockers are equal in their antiarrhythmic efficacy in LQTS.

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