

# β-Blocker Adherence in Familial Long QT Syndrome

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**Background**—Long-term uninterrupted β-blockade significantly reduces cardiac events in long QT syndrome (LQTS).

Despite this, data on nonadherence are scarce and quantified only on the day of cardiac arrest in LQTS literature. We aimed to describe β-blocker adherence, and predictors thereof, among patients with LQTS types 1 and 2.

**Methods and Results**—Electronic health records and pharmacy dispensing data were reviewed for 90 patients with LQTS 1 and 2 who reside in Auckland, New Zealand, during a 34-month period. For each patient, the medication possession ratio (MPR: proportion of follow-up days patients were dispensed β-blocker) was calculated. Adequate adherence was characterized by an MPR ≥0.8 and ideal as MPR=1.0. Clinical and demographic features were assessed to determine whether they predicted adherence. Long-term β-blockers were prescribed to 74 patients (82%). Side effects were described as intolerable by 6 (8%) and their β-blockers were stopped. MPR was calculated in the remaining 68 patients >151.7 patient-years of follow-up. Median MPR was 0.79 (range, 0–1.3). Suboptimal adherence (MPR<0.8) was recorded in 35 (51%). Seven patients (10%) never took up a prescription (MPR=0). Adequate adherence was present in 33 (49%), including 9 (13%) who had ideal adherence. Age, sex, clinical presentation, family history of sudden death, ethnicity, and deprivation index did not predict adherence.

**Conclusions**—Adherence to β-blockers in LQTS is suboptimal in half of those with LQTS 1 and 2. Risk factors for nonadherence could not be identified in our population. Further research into β-blocker adherence is imperative in this high-risk population. (*Circ Arrhythm Electrophysiol.* 2016;9:e003591. DOI: 10.1161/CIRCEP.115.003591)

**Key Words:** long QT syndrome ■ medication adherence ■ patient compliance ■ sudden death ■ risk factor

Medical management of long QT syndrome (LQTS) types 1 and 2 is based on long-term uninterrupted β-blockade because they are known to significantly reduce the risk of all cardiac events.<sup>1–3</sup> This is particularly pertinent for patients with LQTS type 1 because of missense mutations in the C-loops of KCNQ1.<sup>4,5</sup> Despite this, break-through cardiac events continue to occur,<sup>1</sup> and possible reasons for this include lack of adherence at the time of cardiac event,<sup>2</sup> insufficient dose or incomplete effectiveness,<sup>1</sup> and possibly variable efficacy of different β-blockers.<sup>6,7</sup> However, despite the potentially lethal consequence of medication failure, the quantification of β-blocker adherence in this population has never been formally studied.

LQTS patients in general may be at high risk of nonadherence because adherence is generally poorer in chronic conditions, in the young, and particularly during adolescence.<sup>8</sup>

Because medication nonadherence may predispose to sudden death in LQTS, it is important to document barriers to patient uptake of medication. Analysis of adherence is the first step toward this. A new community and hospital pharmacy electronic recording system was established recently in the

Auckland region of New Zealand. Everyone in New Zealand has a unique patient identifier, which is used for all hospital, specialist, and pharmacy visits. In a cohort of LQTS patients for whom β-blockers had been recommended, we aimed to study adherence by assessment of their electronic health records and pharmacy take up-rates to document medication possession ratio (MPR).

## Methods

### Study Design and Patient Cohort

Patients enrolled in the New Zealand Cardiac Inherited Disease Registry who were gene positive for LQTS1 or LQTS2 and who lived in the Auckland District Health Board region (population ≈480 000) were reviewed for this study (n=90; Figure). They had prospectively consented to their data being used for research,<sup>9</sup> and approval from the local ethics committee was also obtained. Patients' electronic health records were reviewed to confirm β-blockers had been recommended. Fifteen patients, in whom β-blockers were never prescribed, were excluded. In one further patient they were only prescribed for the postpartum period, leaving 74 in whom long-term β-blocker therapy was intended. Five of these 74 patients (7%) ceased β-blockers because of documented adverse side effects and one had a left cardiac sympathetic denervation (LCSD) for professed nonadherence before

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### WHAT IS KNOWN

- Beta-blocker therapy greatly reduces risk of syncope and sudden death in familial long QT syndrome types 1 and 2.
- Despite this, no published data exist about adherence to medical therapy in familial long QT syndrome.

### WHAT THE STUDY ADDS

- Beta-blocker adherence is suboptimal in half our patients with long QT syndrome types 1 and 2 and is completely absent in 10%.
- Only 13% of patients had ideal adherence (defined by medication possession ratio of  $>0.8$ ).
- Reasons for lack of adherence remain unidentified.

study commencement (n=1). The remaining 68 patients remained eligible for the study, which commenced either from the patients' first pharmacy dispensation date or from January 1, 2011 (as some eligible patients were primarily nonadherent before commencement of pharmacy records). Data were censored on October 31, 2013 (after a 34-month period) or when the patient had an LCSD performed for nonadherence, whichever occurred first.

### Management Strategy for Patients With LQTS1 and LQTS2

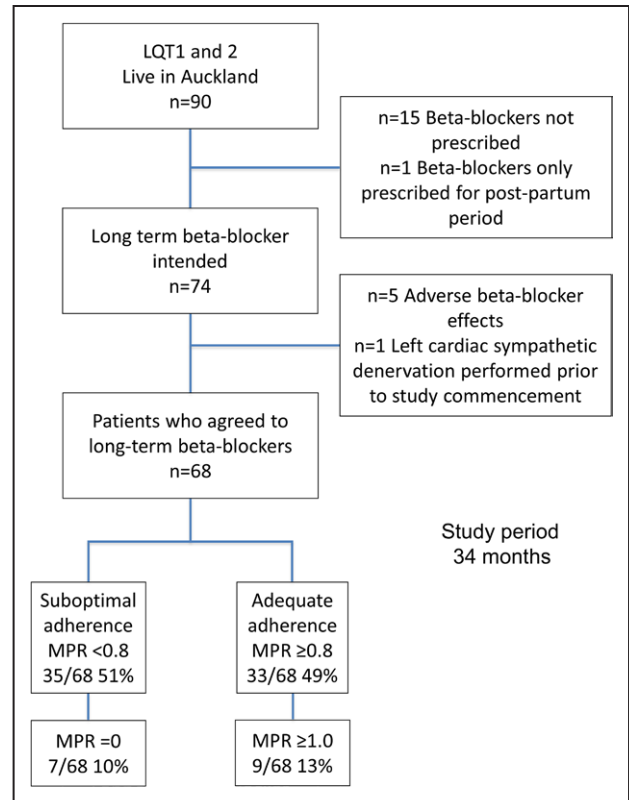
In an effort to achieve optimal adherence in as many of our patients as possible, our approach with both patients and their families is to have a frank and nonjudgmental discussion about medical therapy. We explain the indications for treatment, expected risk reduction, possible adverse effects, and the need for uninterrupted therapy. Patients are invited to commence therapy immediately, take a prescription to commence after further family-based consideration, or to return for another clinic appointment if the patient is uncertain. Once daily preparations are prescribed whenever possible, although this is still not possible in young children who are unable to take tablets. If patients decline  $\beta$ -blocker therapy, profess to an ability to be adherent, or have unacceptable side effects, we discuss LCSD.<sup>10</sup>

We strongly advocate treatment in any patient who has experienced syncope or cardiac arrest or has a C-loop missense LQTS1 mutation and recommend primary prevention in those at risk of developing symptoms. These patients include anyone with a QTc outside the normal range (especially if QTc exceeds 500 ms), boys with LQTS1, women with LQTS2, or anyone participating in high-risk activities (particularly swimming). We offer  $\beta$ -blockers, but do not consider them to be essential, if the QTc is consistently  $<470$  ms and none of these just stated characteristics are present.<sup>11</sup> We review patients as dictated by their particular clinical situation. Where new therapy is initiated or patients are requiring increased support (such as after a new diagnosis or clinical event), patients can be reviewed monthly. Thereafter, during adolescence and childbearing years, annual review is normal, and in very low-risk patients, a 2-year review may be scheduled. Patients are provided 2 separate direct methods of contact and are invited to request a review whenever they feel the need.

### Data Collection

Demographic data including socioeconomic status using the New Zealand Deprivation Index, which is a census-based local domicile 10-point index of deprivation.<sup>12</sup> Clinical information such as genotype, mode and time of presentation, and family history of LQTS and sudden cardiac death was also collected.

The pharmacy data recorded include date of prescription filled, generic and brand drug name, drug dosage, form (eg, tablets or



**Figure.** Study cohort. LQTS1 indicates long QT syndrome; and MPR, medication possession ratio.

syrup), quantity of medication dispensed, administration instructions, and pharmacy name and contact details.

### Pharmacy Outcome of Interest

$\beta$ -Blocker use in the 68 patients who agreed to long-term  $\beta$ -blocker adherence and did not report significant adverse side effects was assessed by the MPR during the study period. This is a common method of calculating medication adherence<sup>13</sup> and is considered to be a reasonable representation of medication consumption.<sup>14</sup> MPR was calculated with a frequently used formula: the number of days' supply of medication dispensed during a specified study period divided by the number of days from the first dispensation to the end of the study period.<sup>13</sup> Adequate adherence was defined as those with  $MPR \geq 0.8$  and ideal  $MPR \geq 1.0$ .<sup>13,14</sup> We also included individuals who appeared to have initial nonadherence, giving an MPR of 0.

### Statistical Analyses

Patient characteristics were summarized using descriptive statistics: continuous data including age and deprivation index are reported as median with interquartile range, and categorical data are reported as frequency with percentages. Categorical data include MPR, ethnicity, family history of sudden death, and clinical presentation. Ordinal logistic regression was used to identify predictors of adherence to  $\beta$ -blockers. Variables considered included age, clinical presentation, family history, ethnicity, and deprivation index and were considered significantly associated with  $\beta$ -blocker adherence when  $P$  value is  $<0.05$ . MPR was grouped into 4 categories: MPR 0 to  $<0.5$ ,  $0.5$  to  $<0.8$ ,  $0.8$  to  $<1.0$ , and  $\geq 1.0$ . Ethnicity was grouped into binary variables: Maori/Pacific Islander versus European/other. Analyses were performed in the statistical package SAS version 9.3 (SAS Institute, Cary, NC) and GraphPad Prism version 6.0e for Mac, GraphPad Software, La Jolla, CA, [www.graphpad.com](http://www.graphpad.com).

## Results

### Clinical Cohort

Sixty-eight patients (including 30 probands) were available for study inclusion because they were expected to be taking  $\beta$ -blockers in Auckland during the study period according to their clinical records (Table 1). No cardiac events were documented during this period.

The initial  $\beta$ -blockers taken by the 61 initially adherent patients were metoprolol controlled release (n=32), nadolol (n=20), atenolol (n=8), and celiprolol (n=1). For initial  $\beta$ -blocker prescribed according to the age group, see Table 2. Seven patients changed to nadolol and 1 patient swapped from nadolol to metoprolol controlled release. In preschool children, twice daily liquid atenolol is most commonly used, transferring to once daily nadolol when they can reliably take a tablet.

Most patients were followed-up regularly in cardiology outpatient appointments: mean of 2.4 visits/patient during the 34-month follow-up period (range 0–6). The total number of cardiology encounters (including inpatient admissions and outpatient investigations when a cardiologist was seen [excluding implantable cardioverter defibrillator checks and echocardiograms for example]) was a median of 2 per patient during the follow-up period (range, 0–8). Any additional private practice encounters (which are uncommon) were not recorded.

### Medication Adherence

#### Medication Possession Ratio

The total number of study days was 55374 (151.7 patient-years; median: 2.7; interquartile range: 1.4–3.1 years). Median MPR was 0.79, ranging from 0 to 1.3. Thirty-five patients (51%) had suboptimal adherence (MPR<0.8) including 7 who never filled a prescription (MPR=0). Thirty-three (49%) had adequate adherence (MPR>0.8) including 9 (13%) with ideal adherence (MPR $\geq$ 1.0; Table 1).

#### Patients With Low Adherence

In patients with suboptimal adherence, hospital records show that many attended appointments and answered direct questions about adherence and adverse drug effects positively. However, their corresponding electronic dispensing records suggest that no medications had been dispensed, and therefore that the affected person had not been adherent. Furthermore, in 23 patients whose dispensation data would suggest a period of nonadherence, 26 outpatient cardiology appointments occurred where an opportunity to provide a new prescription existed.

#### Primary $\beta$ -Blocker Nonadherence

Of 68 patients, 7 (10%) were primarily nonadherent. There were 5 females, and 4 patients with LQTS1. Presentations included cardiac arrest (3), syncope (1), and family screening (3). All 7 had a family history of sudden cardiac death, and their age ranged between 14 and 58 years (median 28). We contacted these 7 patients after the end of the study, with the permission of their supervising clinicians. Rationale for non-adherence fell into 3 main categories: first the disorganized

**Table 1. Demographic and Clinical Details of 68 Patients With LQTS1 and LQTS2 in Whom  $\beta$ -Blocker Adherence Was Studied**

		N (%) or Median (IQR)	N(%) or Median (IQR) With MPR<0.8
Females		49 (72)	26 (38)
KCNQ1		44 (65)	26 (38)
KCNH2		24 (35)	9 (13)
Age at end of the study period, y		27 y (15–48); (min=11 mo, max=73 y)	24 y (15–42); (min=2y, max=73 y)
	0 to 4	2 (3)	1 (1)
	5 to 18	22 (32)	12 (18)
	>18	43 (63)	22 (32)
Mode of presentation	Family screening	38 (56)	18 (26)
	Incidental diagnosis	8 (12)	4 (6)
	Syncope	16 (23)	9 (13)
	Cardiac arrest	6 (9)	3 (4)
Deprivation Index, <sup>12</sup> in deciles (wealthy areas have a lower number)	1	10 (15)	3 (4)
	2	8 (12)	5 (7)
	3	8 (12)	6 (9)
	4	7 (10)	3 (4)
	5	1 (1)	1 (1)
	6	6 (9)	5 (7)
	7	2 (3)	1 (1)
	8	2 (3)	0 (0)
	9	11 (16)	4 (6)
	10	13 (19)	7 (10)
Ethnicity	Maori	9 (13)	5 (7)
	Pacific Islander	3 (4)	2 (3)
	European	52 (77)	27 (40)
	Other	4 (6)	1 (1)
Family history of sudden cardiac death	Yes	44 (65)	21 (31)
	No	24 (35)	14 (21)
MPR	0 to <0.5	19 (28)	N/A
	0.5 to <0.8	16 (24)	N/A
	0.8 to <1.0	24 (35)	N/A
	$\geq$ 1.0	9 (13)	N/A

IQR indicates interquartile range; LQTS, long QT syndrome; max, maximum; min, minimum; MPR, medication possession ratio; and N/A, not applicable.

patient, one of whom has hypoxic encephalopathy after an LQTS-related cardiac arrest. These 2 patients have since had an LCSD performed. Second, 3 patients had a fear of medication side effects, and finally 2 perceived their risk to be low (contrary to the views of their cardiologists). Two of these patients have since commenced regular  $\beta$ -blockade and one now has an implantable cardioverter defibrillator.

**Table 2. Initial  $\beta$ -Blocker Prescribed According to the Age Group**

	$\leq 4$ y	5–19 y	20–40 y	$\geq 41$ y
Atenolol	3	2	0	3
Nadolol	0	15	3	2
Metoprolol controlled release	0	7	11	14
Celiprolol	0	0	0	1

Twenty-two patients were prescribed  $\beta$ -blockers for the first time after the study commenced. Median time between the first prescription and dispensation was 5 days (range, 1–100 days), 4 (18%) took  $>1$  month to obtain the first prescription.

### Adherence in a High-Risk Subset

We used the presence of an implantable cardioverter defibrillator to denote a group of high-risk patients. There were 17 such patients. Mean MPR was 0.58 (range, 0.0–1.3), and MPR was normally distributed. Suboptimal adherence was present in 11 patients, 4 of whom have had an LCSD.

### Predictors of $\beta$ -Blocker Adherence

No studied variables, including length of follow-up, could be shown to be related to compliance with  $\beta$ -blocker medical therapy (Table 3).

## Discussion

This study shows adherence to  $\beta$ -blockers is suboptimal in a large percentage of people in Auckland with LQTS1 and LQTS2, and it is completely absent in 10%.

There is no perfect way to study medication adherence; each technique has its weaknesses. Even methods that electronically record date and time of medication canister openings and pill counts do not prove the tablet is swallowed, and electronically or directly observing therapy, quantifying adherence during a clinical trial, or even closely monitored participation in an international registry, may itself encourage unnaturally good adherence. A questionnaire-based approach relying on subjective interpretation or recollection may influence the patient to produce results, which they feel would satisfy the clinician.

This study is thus flawed, although it may use the best technique available. Although it is unlikely that patients would have obtained medication from a pharmacy outside the electronic record zone, we can neither know whether our patients sourced medication from elsewhere, including other family members, nor whether tablets bought were then consumed. However, it does seem reasonable to assume that most people take their own medications, rather than those of others. An important advantage of this study is that no intervention that might artificially elevate adherence was used. It is also a population-based sample, rather than a hospital- or physician-based sample, with a widespread social demography. It also comes from a public health system where health records and pharmacy dispensing records are linked.

The study results are striking and concerning. Perhaps we should not be surprised given that we know  $\beta$ -blocker

adherence after coronary syndromes is generally poor, with adherence at 3 years of post myocardial infarction assessed at 48% to 64%.<sup>15,16</sup> However, in LQTS literature, beyond documenting that poor adherence occurs on days of cardiac arrest, which might therefore be a consequence of medication failure,<sup>2</sup> quantification of general  $\beta$ -blocker adherence is generally absent. Some registry data in LQTS assure us that good adherence tends to ensure good outcome, whereas other research excluded known noncompliant patients from their cohort when discussing  $\beta$ -blocker efficacy.<sup>7</sup> Nonadherence may be similar among the different  $\beta$ -blocker types,<sup>6</sup> but adherence with more complex (twice daily) regimens tends to be lower than simple (daily) regimens, so it seems logical where possible to use a preparation, which can be given once a day.<sup>17</sup> This study is too small to address this question.

We could not identify any clinical or demographic features that predict patient adherence. Others have found in New Zealand that younger aged patients (35–45 versus 55–64 years) and those of Maori or Pacific ethnicity (versus those of European descent) are less likely to have adequate adherence.<sup>14</sup> Even those with severe disease, from affluent social deciles, commonly did not adhere to their  $\beta$ -blocker therapy. This seems surprising, and clearly needs to be evaluated further. There is now a pressing need to discover the reasons for nonadherence in this population.

Readers might wonder whether there is something about our service or population, which would make nonadherence more likely. On the positive side, specialist consultations are free, and prescription costs are low: \$5 NZD (\$3.30 USD) per item and are free for children  $<12$  years of age and those who are unemployed or in financial hardship. Auckland city has a well-developed cardiac genetic service, with one of the highest detection rates of LQTS in the world,<sup>9</sup> and well-described protocols for management.<sup>18</sup> On the negative side, national

**Table 3. Relationship of Clinical and Demographic Features to  $\beta$ -Blocker Adherence**

Predictor	Clinical and Demographic Variables	Odds Ratio*	95% Confidence Limit	P Value
Clinical presentation	Cardiac arrest vs family screening	2.93	0.52–16.57	0.59
	Syncope vs family screening	1.47	0.48–4.49	
	Incidental diagnosis vs family screening	0.89	0.19–4.10	
Deprivation Index (10-point scale)		0.94	0.80–1.09	0.39
Family history of sudden cardiac death	No versus Yes	1.11	0.40–3.03	0.84
Age, y		0.99	0.96–1.01	0.27
Ethnicity	European/Other vs Maori/Pacific	0.58	0.15–2.82	0.43

\*The probability of poorer compliance was modeled using ordinal logistic regression.

regulations dictate that physicians can only prescribe a medication for 3 months at a time. A repeat prescription must be obtained to continue even when the medication is long term. This process may be semiautomated, usually through the family practitioner, but may well be a practical deterrent, although it cannot explain the 10% who never even started to take their  $\beta$ -blockers.

This study confirms that our ability to accurately assess patient adherence in clinic is low. This is most noticeable in the discrepancy between patients' positive responses to questions about medication adherence when they were not in possession of medication according to their electronic dispensation records.

Further studies with a wider population base are required, and back up questionnaires will aim to document patient's attitude to their condition, their medication, and their perceived medication adherence.

### Limitations

Although all pharmacies within the Auckland region are currently contributing to dispensing data, patients may have collected medicine outside this geographical region, and thus been to a pharmacy that had not yet enrolled in the dispensing records scheme. We ensured that all patients had some documented interaction with Auckland region health care during periods of apparent nonadherence (manifested by either an appointment or other medication dispensation), and used MPR, an average measure of adherence over time, rather than considering adherence at various time points during follow-up. Furthermore, these 68 individuals were the total population available, and therefore differences would need to be large to be able to demonstrate them statistically.

Using pharmacy dispensing data assumes a prescription collected is a prescription consumed as directed on the label. Variations to this include patient nonadherence (either deliberate or unintentional), or when the prescriber has instructed the patient to modify the dose (eg, dose increases after a certain time period).

### Conclusions

This first formal study of adherence to  $\beta$ -blockade therapy in LQTS in a country with a public health service and low-prescription costs reveals that adherence is ideal in only a small minority and is poor or even absent in half. The cornerstone of therapy in LQTS has an Achilles heel. There is much work to be done to find out how common this problem is elsewhere and what can be done to improve it.

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### Disclosures

None.

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