The congenital long QT syndromes (LQTS [cumulative incidence 1:2,000]) are individually distinct but exhibit a common phenotype of QT-interval prolongation and sudden death risk. Potassium channel mutations, KCNQ1 (LQTS1) and KCNH2 (LQTS2), account for approximately 60% of cases. Beta-blockers have long been the mainstay of therapy, dramatically reducing syncope and death (1). Pharmacologically, beta-blockers blunt beta-adrenergic receptor-mediated sympathetic stimulation, but have varying half-lives and extracardiac effects contingent upon beta-isof orm specificity and lipophilicity (Table 1).

Although retrospective, several prior studies have compared the efficacy of different beta-blockers in treating LQTS (Table 2) (2–6). In this issue of the Journal, Chockalingham et al. (7) present a compelling argument that the pharmacologic differences among 3 commonly prescribed beta-blockers—propranolol, nadolol, and metoprolol—significantly impact arrhythmic risk in genotype confirmed LQTS1 and LQTS2 (7). A multicenter cohort of 382 patients treated with beta-blockers was assembled. The primary composite endpoint included abrupt syncope, near drowning, seizure episodes, or aborted cardiac arrest. The investigators found that: 1) propranolol shortened QTc more than nadolol or metoprolol; 2) QTc shortening inversely correlated with cardiac events; and 3) metoprolol protected less than propranolol or nadolol.

First, the researchers compared the QTc before beta-blocker with on-therapy QTc. The propensity for propranolol to shorten the QTc was most evident for baseline QTc exceeding 480 ms. The QTc shortening did not appear artificial owing to an imperfect correction formula, as rate slowed to a similar degree with each beta-blocker. To confirm differential QTc shortening, they exploited the transition of 14 patients (11 LQTS1 and 3 LQTS2) from propranolol to metoprolol. After switching, QTc increased from 447 ± 20 ms to 464 ± 39 ms. Notably, because the therapy transition occurred at 11 years and the comparison propranolol ECG was recorded several years earlier, interim hormonal changes could be operative (8). Data are limited regarding differential QTc effects of beta-blockers in LQTS. In 1 small mechanistic study, propranolol did not shorten QTc under baseline conditions (9). However, body surface electrode recordings uncovered favorable changes in spatial and transmural dispersion of repolarization; propranolol-mediated QTc shortening was noted during epinephrine infusion. Further reinforcing the limitation of using QTc alone for arrhythmic risk, and the complexity of arrhythmia occurrence in LQTS, is the observation that components of the T wave can occur with adrenergic stimulation or blockade (10).

Second, Chockalingham et al. (7) observed that QTc shortening was inversely proportional to cardiac events. This observation supports a previous observation made by Moss et al. (1) in LQTS patients; they found that patients initiated on beta-blocker therapy who had a reduction in QTc tended to have a favorable outcome. The inverse relationship between QTc and sudden cardiac death has also been observed in non-LQTS patients with coronary artery disease (11), further underscoring the role that transmural dispersion of repolarization has in ventricular arrhythmias. The ability to directly modify QTc and seemingly decrease the risk of cardiac events focuses attention on whether other agents that can shorten QTc, particularly in LQTS3 (12), would reduce arrhythmic events. In addition, one could hypothesize that manipulation of QT might have benefits in other situations, such as ischemic heart disease. Clearly, our understanding is incomplete, in that nadolol did not shorten

*Correlates with ability to cross blood-brain barrier. †Half-life of principal metabolite, 4-hydroxy propranolol.
QTc, like metoprolol and unlike propranolol, yet led to favorable outcomes, unlike metoprolol.

Third, Chockalingham et al. (7) found metoprolol inferior to both propranolol and nadolol for the prevention of cardiac events in patients with LQT1S and LQT2S. At 10 years of follow-up, patients receiving either propranolol or nadolol had an event-free survival of 91% as compared with 60% on metoprolol. Although retrospective, these results do argue against the use of metoprolol and in favor of either nadolol or propranolol in the treatment of LQTS. In addition, because considerations of convenience and compliance drove the transition from short-acting propranolol to metoprolol, such changes must not be undertaken lightly. In this regard, nadolol had excellent efficacy and possesses pharmacokinetics compatible with once-daily dosing (Table 1). As 99% of propranolol-treated patients used the short-acting preparation, it is not clear whether extended-release propranolol is an acceptable alternative.

While the Chockalingham et al. (7) deserve recognition for their important observations, several limitations must be emphasized. First, owing to the nonrandomized nature of this retrospective analysis, there were significant differences in baseline clinical characteristics between the different treatment groups, including sex, history of syncope, baseline QTc, age at which therapy was started, and on-therapy heart rate. Three other aspects of the patient population need to be emphasized: 1) the baseline mean QTc for the study population was 472 ms, indicating that a significant proportion of the patient population (64%) had a normal or borderline QTc; 2) only 27% of the study population had had symptoms before therapy, roughly correlating with the number of patients with a prolonged QTc; and 3) a significant number of patients switched beta-blockers during follow-up, an observation capitalized upon by the investigators, as noted. Next, caution is needed in generalizing about preferred therapy for LQTS, as LQT1, 2, and 3 (and other subtypes) represent multiple syndromes with unique characteristics. Even within subtypes, risk and beta-blocker benefit may vary by mutation site, type, and other factors (5). For example, LQT1 patients harboring C-loop mutations appear to respond more favorably to beta-blockers (5). Intriguingly, mutation of the sodium-channel blocker binding site can affect the ability of propranolol to block sodium current (13).

In conclusion, Chockalingham et al. (7) provide some of the most compelling evidence to date that “not all beta-blockers are equal.” Although randomized trials are formidable involving rare conditions like LQTS, additional data on differential benefit of beta-blockers from registries would be helpful. Moreover, these findings suggest the potential for reducing sudden death by QTc modulation in common acquired conditions exhibiting QTc prolongation and/or increased transmural dispersion of refractoriness.

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REFERENCES


### Table 2: Studies Evaluating and Comparing Beta-Blockers in Long QT Syndrome

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>Genotype</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moss (1)</td>
<td>LQT1, 2, 3 (n = 860)</td>
<td>QTc shortening associated with favorable outcome; no apparent differential effect among beta-blockers</td>
</tr>
<tr>
<td>Chatrath (6)</td>
<td>LQT1, 2, 3 (n = 28)</td>
<td>Atenolol associated with adverse outcome</td>
</tr>
<tr>
<td>Vincent (2)</td>
<td>LQT1 (n = 216)</td>
<td>No QTc shortening; beta-blocker treatment failures attributed to noncompliance and QTc-prolonging drugs; 84% of experience with propranolol or nadolol; no apparent differential effect among beta-blockers</td>
</tr>
<tr>
<td>Barsheshet (5)</td>
<td>LQT1 (n = 860)</td>
<td>Beta-blockers more efficacious for C-loop mutations</td>
</tr>
<tr>
<td>Priori S (3)</td>
<td>LQT1, 2, 3 (n = 335)</td>
<td>Beta-blockers more efficacious in LQTS 1 than in 2 or 3</td>
</tr>
<tr>
<td>Shimizu (9)</td>
<td>LQT1, 2 (n = 22)</td>
<td>Propranolol reduced QTc during epinephrine infusion but not baseline state</td>
</tr>
<tr>
<td>Goldenberg (4)</td>
<td>LQT1, 2</td>
<td>Atenolol more effective in LQT1; nadolol in LQT2; metoprolol less effective in both, but HR = 0.69 for all beta-blockers</td>
</tr>
</tbody>
</table>

HR = hazard ratio; QTc = long QT syndrome; QTc = corrected QT interval.

Key Words: adrenergic beta-antagonists • long QT syndrome • sudden cardiac death • syncope.