Beta-blocker therapy for long QT syndrome and catecholaminergic polymorphic ventricular tachycardia: Are all beta-blockers equivalent?

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Congenital long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) are 2 of the most common cardiac channelopathies. Among patients who have experienced an LQTS-triggered cardiac event (arrhythmic syncope, arrhythmic syncope followed by seizures, or aborted cardiac arrest), the untreated natural history is grim, with >50% mortality at 15 years.1 Today, however, early diagnosis facilitates implementation of appropriate therapy, and the incidence of sudden death has dropped significantly.1 Treatment strategies for these conditions have expanded to include drug therapy, denervation surgery, or implantable devices.2,3 Importantly, drug therapy with beta-blockers represents the therapeutic mainstay for both LQTS and CPVT. The 2013 HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia and the 2015 ESC Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Death call for universal beta-blocker therapy as a first approach in all patients with either LQTS or CPVT, except in cases in which the patient presents with LQTS/CPVT-triggered sudden cardiac arrest.2,4 Table 1 shows how beta-blocker usage is considered first-line therapy in these channelopathies.7,4 The risk of limiting access to nadolol

The recent discontinuation of nadolol availability in the United Kingdom (UK) is the impetus behind this clinical document. Our goal is to help clinicians understand the importance of beta-blocker therapy in these 2 genetic disorders, as well as to provide clinical guidance on the choice of agents. Nadolol, when available, has been the preferred beta-blocker used by the largest LQTS/CPVT specialty centers throughout the world for the past 25 years.

Nadolol was first made available clinically in 1979, with the first generic product appearing on the market in 1993.5 An increase in research on LQTS and CPVT response to beta-blockers has concurrently occurred, and studies suggest that nadolol is more efficacious compared to beta1-selective blockers.5

This therapeutic paradigm is under threat in several countries, despite being recognized by channelopathy experts around the world, and the drug is at risk for disappearing from the market. The impact of this development could be profound. For this reason, the Heart Rhythm Society (HRS) formed a task force to investigate the clinical implications. As part of these efforts, a survey was sent to both pediatric and adult heart rhythm specialists, mostly in North America and Europe. More than 70% of respondents (n = 109) use nadolol in at least 75% of their patients with LQTS. Thus, the potential lack of availability of nadolol would necessitate a major change in practice patterns.
Methodologic aspects of data on drug efficacy in LQTS and CPVT

No randomized clinical trials (RCTs) addressing the comparative efficacy of different beta-blockers for the treatment of these conditions exist. The lack of RCTs for both LQTS and CPVT has been documented recently by a Cochrane Review aimed at defining the role of medical therapy vs implantable cardioverter–defibrillator (ICD) therapy in channelopathies.6 The authors concluded that such a review was not possible secondary to the lack of RCTs that would address the methodology. This may explain the conflicting results of a much larger study (1530 patients) from the International Registry of LQTS conducted by Moss and collaborators.7 In this study, when the LQTS genotypes were grouped together, atenolol, metoprolol, propranolol, and nadolol all appeared equally effective. However, when the efficacy of different beta-blockers was compared to other therapies, although propranolol and nadolol had comparable efficacy, metoprolol was significantly less effective in protecting from ventricular fibrillation (VT/VF). The data that follow represent the clinical evidence from studies that have sought to evaluate the relative efficacy of specific beta-blockers for LQTS and CPVT.

Evidence-based data on the efficacy of beta-blockers in LQTS

The idea that beta-blockers are effective in reducing life-threatening arrhythmias in LQTS is well established. However, in the vast majority of investigations, therapy “on beta-blockers” has been compared to “no therapy” or “other therapies,” with only occasional exploration of differences in efficacy among the different beta-blockers.7,8 Recently, 3 studies have compared the efficacy of beta-blockers among patients with the 3 most common LQTS genotypes: LQT1, LQT2, and LQT3. The first of the 3 studies was performed in a relatively small population of 382 patients treated with propranolol (n = 134), metoprolol (n = 147), or nadolol (n = 101).9 The overall results demonstrated that although propranolol and nadolol had comparable efficacy, metoprolol was significantly less effective in protecting from events. It should be noted that the study did not consider important covariances that might have affected the outcome, such as the duration of the QT interval, discrepant number of patients within each group, and the occurrence of clinical events.

This may explain the conflicting results of a much larger study (1530 patients) from the International Registry of LQTS conducted by Moss and collaborators. In this study, when the LQTS genotypes were grouped together, atenolol, metoprolol, propranolol, and nadolol all appeared equally effective. However, when the efficacy of different beta-blockers was
analyzed individually for LQT1 and for LQT2, it became evident that nadolol was the most effective among the more severely affected group of LQT2 patients. These data are quite relevant because it is well known that response to beta-blocker therapy is greater among LQT1 patients compared to LQT2 and LQT3 patients, especially in LQT2 patients when QTc is $>500$ ms.\textsuperscript{10} Thus, it has become routine practice in most genetic disease clinics for the most severe cases to be preferentially managed with nadolol. Finally, beta-blocker therapy has been shown to reduce risk even among patients with LQT3.\textsuperscript{11} However, differential efficacy among the individual beta-blockers has not been examined.

Given the absence of RCTs plus the limitations of retrospective single-center and registry studies, practicing clinicians tend to rely on the experience of LQTS/CPVT specialists. There is a strong experiential preference throughout the world toward using nadolol as the beta-blocker of choice in LQTS and CPVT. The international observational experience clearly demonstrates that the apparent protective effect of the non-selective beta-blockers (nadolol and propranolol) far exceeds the efficacy observed with the beta₁-selective beta-blockers.

Limited data comparing nadolol and propranolol are available. Whereas propranolol may be preferable to beta₁-selective agents, the limited comparative data and less favorable pharmacokinetic profile raise concerns that it may be inferior to nadolol. Abu-Zeid et al\textsuperscript{12} found differences in the likelihood of recurrent events in patients with LQTS, with propranolol therapy being the least effective. Ease of dosing may also limit the enthusiasm for propranolol because it has a shorter half-life than nadolol. Although an extended-release preparation of propranolol is available, many younger children are too small for the dosing available with this preparation.

Thus, there is substantial consensus among experts that nadolol is the preferred effective drug therapy in LQTS, and, whenever tolerated, it should be administered as a first-choice therapy in patients with LQTS. The dosage that is usually adopted is 1–1.5 mg/kg/day administered once a day in patients ≥12 years of age and usually divided twice daily in infants and children. The convenient once-daily administration is also likely to improve compliance. Whereas the preference for nadolol as first-choice agent is established among experts, no conclusive recommendation can be provided to identify the next best option, although the HRS survey and the largest LQTS centers have used propranolol in this scenario.

Evidence-based data on beta-blockers in CPVT

There are few data to guide clinicians about the comparative efficacy of different beta-blockers in CPVT, as well. CPVT is a relatively rare disease compared to LQTS, and the methodologic issues surrounding the LQTS studies are even greater when considering CPVT.

Review of the literature shows that beta-blockers in CPVT reduce the number of arrhythmic events compared to no therapy or Class I antiarrhythmic drugs.\textsuperscript{13,14} However, CPVT-triggered breakthrough cardiac arrhythmic events often occur in patients who are compliant on beta-blockers. CPVT patients often require additional therapies, such as left cardiac sympathetic denervation, flecaïnide, or ICD therapy.\textsuperscript{15–16}

In this context, the relatively small study by Hayashi et al\textsuperscript{13} provides observational data in support of the superiority of nadolol compared to other beta-blockers. The authors reported on 81 CPVT patients with an average follow-up of 8 years. They showed that patients taking beta-blockers had fewer events than patients without therapy (breakthrough rate of 58% in 8 years in the untreated group vs 27% in the group treated with beta-blocker; $P = .001$). Nadolol was superior to the other beta-blockers in preventing arrhythmias during therapy (19% with breakthroughs while taking nadolol vs 39% during treatment with other beta-blockers). Remarkably and importantly, multivariable analysis showed that being treated with a beta-blocker other than nadolol was an independent risk factor for breakthrough CPVT-triggered cardiac events (hazard ratio 3.12, 95% confidence interval 1.16–8.38; $P = .002$). The authors point to lack of compliance with medication as an important cause of recurrence of arrhythmic events in the population. In this respect, nadolol’s pharmacokinetic properties enabling once-a-day administration may provide a therapeutic advantage compared to the multiple administrations required with most of the other beta-blockers.

Very recently, a small prospective study further supported the contention that nadolol is more effective than other beta-blockers in preventing arrhythmias elicited during exercise stress test.\textsuperscript{17} In this study involving 34 patients with CPVT, the authors compared the burden and complexity of arrhythmias observed during exercise stress testing that was performed before drug initiation after $>6$ weeks on a beta₁-selective beta-blocker and after $>6$ weeks on nadolol. To compare arrhythmic events, a score was created to assign more points to more complex arrhythmic episodes. Overall, the score while taking a beta₁-selective beta-blocker was not significantly different than the score without therapy. In contrast, the score while being treated with nadolol was significantly better. From a methodologic point of view, albeit small, this study has the merit of being prospective. However, the key limitation is that the endpoints are arrhythmic events spanning from premature ventricular complexes to hemodynamically tolerated ventricular tachycardias and therefore do not include life-threatening arrhythmic events. Nevertheless, these data support the concept that nadolol is superior to other beta-blockers and that during exercise stress testing, physicians should be able to observe the reduction of arrhythmias compared to the predrug test. In case of limited efficacy, the dosage of beta-blockers may be increased until tolerated to achieve the most protective levels. In this respect, the studies of Priori et al\textsuperscript{15} and Hayashi et al\textsuperscript{13} both have reported the safe use of doses of nadolol that reach 2 mg/kg/day.

If nadolol is not available, unfortunately there is no ideal alternative. Therefore, we recommend that the choice should be guided by the ability of the beta-blocker to suppress ventricular ectopy on the exercise test. As in LQTS, when nadolol has not been available or tolerated, most large CPVT centers use propranolol. For propranolol, the targeted dosing
is 3–4 mg/kg/day generally divided 3 times daily in children and twice daily in adolescents and adults when using the extended-release preparations of propranolol (propranolol ER or Inderal LA).

There is strong consensus among the authors that nadolol is the preferred antiarrhythmic, antiadrenergic therapy for CPVT patients. Whereas the conventional dosage is that of 1 mg/kg per day, data that support the safety of the highest tolerated dosage indicate the potential to double the standard recommended regimen.

The HRS is concerned that if nadolol becomes difficult to obtain or unavailable, patients with LQTS or CPVT will be at greater risk for sudden death, and that clinicians will be forced to consider otherwise unnecessary and more aggressive treatment options such as ICD therapy. Importantly, this document is not intended to serve as a blind defense of nadolol or to supplant rigorous, evidence-based medicine in general. Although the gold standard of RCTs would be preferable to other beta-blockers in these diseases, it is unlikely that these studies will be performed because there is no driving incentive for a randomized trial for this class of medication to treat these uncommon syndromes.

Thus, it is important to look to expert opinion for guidance in this matter. There is unanimous agreement among the writing committee members that nadolol is considered a frontline and efficacious agent for LQTS and CPVT among patients of all ages at risk for sudden death. Thus, HRS believes that this is an important issue to raise in the general community and urges for the continued availability of nadolol for our vulnerable patients with LQTS and CPVT.

Appendix
Supplementary data
Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2016.09.012.

References