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**Beta Blocker Therapy for Long QT Syndrome and Catecholaminergic Polymorphic Ventricular Tachycardia: Are all beta blockers equivalent?**

Developed and endorsed by the Heart Rhythm Society.

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Congenital long QT syndrome (LQTS) and catecholaminergic polymorphic ventricular tachycardia (CPVT) are two of the most common cardiac channelopathies. Among patients who have experienced a 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. Today, however, early diagnosis facilitates implementation of appropriate therapy and the incidence of sudden death has dropped significantly. Treatment strategies for these conditions have expanded to include drug therapy, denervation surgery, or implantable devices.

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 cardiac death call for universal beta blocker therapy as a first approach in all patients with either LQTS or CPVT, except in cases where the patient presents with LQTS/CPVT-triggered sudden cardiac arrest. Table 1 illustrates how beta blocker usage is considered as first line therapy in these channelopathies.

### 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 two genetic disorders, as well as to provide clinical guidance on the choice of agents. Nadolol, when available, has been the preferred beta blocker utilized 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. An increase in research on LQTS and CPVT response to beta-blockers has concurrently occurred and studies suggest that nadolol is more efficacious when compared to beta-1 selective blockers.

This therapeutic paradigm is under threat in several countries, despite being recognized by channelopathy experts around the world, and the drug is at risk of 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, largely 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.

### Methodological 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 versus implantable cardioverter defibrillator (ICD) therapy in channelopathies. The authors concluded that such a review was not possible secondary to the lack of RCTs that would fit the methodology of Cochrane Reviews in LQTS and CPVT. As a consequence, the evidence that beta blockers are effective in reducing cardiac events in patients with either LQTS or CPVT is drawn from single expert center experiences or multicenter registries that are collected in different parts of the world with heterogeneous methodologies. This evidence is complicated by methodological limitations inherent in data derived from registries. Registries may have different criteria for inclusion (patients cared for in community vs tertiary...
care center; retrospective vs. prospective data vs. combination). These problems are common to the study of rare diseases and explain how practice guideline development may accept expert opinion, small single site studies, and registry data.

For these reasons, LQTS and CPVT investigators, conscious of the methodological limitations of data collections in registries, have been careful in attempting comparative analysis on the efficacy of the different beta blockers and on the definition of the appropriate dosage. To compensate for the small series of patients, a solid statistical methodology is mandatory and adjustment for the characteristics of the populations under study is a critical component of the analysis.

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, three studies have compared the efficacy of beta blockers among patients with the three most common LQTS genotypes: LQT1, LQT2, and LQT3. The first of the three 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 while 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 co-variates 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 when compared to LQT2 and LQT3 patients, especially in LQT2 patients when the QTc is greater than 500 msec.(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.(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 towards 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 beta 1-selective beta blockers.
There is limited data available comparing nadolol and propranolol. Whereas propranolol may be preferable to beta 1-selective agents, the limited comparative data and less favorable pharmacokinetic profile raise concerns that it may be inferior to nadolol. Abu-zeitone and colleagues found differences in likelihood of recurrent events in patients with LQTS, with propranolol therapy being the least effective. (12) Ease of dosing may also limit the enthusiasm for propranolol, as it has a shorter half-life than nadolol. While 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 is little data to guide clinicians about the comparative efficacy of different beta blockers in CPVT, as well. CPVT is a relatively rare disease when 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 as compared to no therapy or class 1 antiarrhythmic drugs. (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, flecainide, or ICD therapy. (14-16)

In this context, the relatively small study by Hayashi provides observational data in support of the superiority of nadolol as compared to other beta blockers. The authors reported on 81 CPVT patients with an average follow-up of eight years. (13) They showed that patients on beta blockers had less events than patients without therapy (breakthrough rate of 58% in eight years in the untreated group versus 27% in the beta blocker treated group; p=001). Nadolol was superior to the other beta blockers in preventing arrhythmias during therapy (19% with breakthroughs while on nadolol versus 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 (HR 3.12 CI 1.16 to 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 therapeutic advantage as compared to 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. (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 on a beta 1-selective beta blocker was not significantly different than the score off therapy. In contrast, the score while
being treated with nadolol was significantly better. From a methodological 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 VTs and therefore not including 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 as compared to the pre-drug 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 and Hayashi et al have both reported the safe use of doses of nadolol that reach 2mg/kg/day.(13,15)

If nadolol is not available, unfortunately there is no ideal alternative. Therefore, we recommend that the choice should be guided by 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 utilize propranolol. For propranolol, the targeted dosing is 3-4 mg/kg/day generally divided three 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, anti-adrenergic 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 Heart Rhythm Society is concerned that if nadolol becomes difficult to obtain or unavailable, patients with LQTS or CPVT will be at greater risk of 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. While the gold standard of RCTs would be preferable to answer the question of whether nadolol is indeed superior to other beta blockers in these diseases, it is unlikely that these studies will be performed as 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 front line and efficacious agent for LQTS and CPVT among patients of all ages at risk of 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.
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**Table 1.**

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death(4)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Class</th>
<th>Level of evidence*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LONG QT SYNDROME (LQTS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blockers are recommended in patients with a clinical diagnosis of LQTS.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Beta blockers should be considered in carriers of a causative LQTS mutation and normal QT interval.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td><strong>CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blockers are recommended in all patients with clinical diagnosis of CPVT based on the presence of documented spontaneous or stress induced ventricular arrhythmias.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Therapy with beta blockers should be considered for genetically positive family members even after a negative exercise stress test.</td>
<td>IIa</td>
<td>C</td>
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</tbody>
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2013 HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes(2)

<table>
<thead>
<tr>
<th>Condition</th>
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<th>Level of evidence*</th>
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<tbody>
<tr>
<td><strong>LONG QT SYNDROME (LQTS)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blockers are recommended in patients with a clinical diagnosis of LQTS.</td>
<td>I</td>
<td>Not Available</td>
</tr>
<tr>
<td>Beta blockers <strong>are recommended</strong> in patients with a diagnosis of LQTS who are: a. Asymptomatic with QTc ≥ 470 ms and/or b. Symptomatic for syncope or documented ventricular tachycardia/ventricular fibrillation (VT/VF).</td>
<td>IIa</td>
<td>Not Available</td>
</tr>
<tr>
<td><strong>CATECHOLAMINERGIC POLYMORPHIC VENTRICULAR TACHYCARDIA (CPVT)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta blockers <strong>are recommended</strong> in all symptomatic patients with a diagnosis of CPVT.</td>
<td>I</td>
<td>Not Available</td>
</tr>
<tr>
<td>Beta blockers <strong>can be useful</strong> in carriers of a pathogenic CPVT mutation without clinical manifestations of CPVT (concealed mutation-positive patients).</td>
<td>IIa</td>
<td>Not Available</td>
</tr>
</tbody>
</table>

*Note, the 2013 consensus statement did not require or provide the level of evidence for its recommendation classes.*