Risk of Recurrent Cardiac Events After Onset of Menopause in Women With Congenital Long-QT Syndrome Types 1 and 2

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Background—Women with congenital long-QT syndrome experience an increased risk for cardiac events after the onset of adolescence that is more pronounced among carriers of the LQT2 genotype. We hypothesized that the hormonal changes associated with menopause may affect clinical risk in this population.

Methods and Results—We used a repeated-events analysis to evaluate the risk for recurrent syncope during the menopause transition and postmenopausal periods (5 years before and after the age at onset of menopause, respectively) among 282 LQT1 (n = 151) and LQT2 (n = 131) women enrolled in the Long-QT Syndrome Registry. Multivariate analysis showed that the risk for recurrent syncope (n = 150) among LQT2 women was significantly increased during both menopause transition (hazard ratio, 3.38; \(P = 0.005\)) and the postmenopausal period (hazard ratio, 8.10; \(P < 0.001\)) compared with the reproductive period. The risk increase was evident among women who did or did not receive estrogen therapy. In contrast, among LQT1 women, the onset of menopause was associated with a reduction in the risk for recurrent syncope (hazard ratio, 0.19; \(P = 0.05\); \(P = 0.02\) for genotype-by-menopause interaction). Only 22 women (8%) experienced aborted cardiac arrest or sudden cardiac death during follow-up. The frequency of aborted cardiac arrest/sudden cardiac death showed a similar genotype-specific association with the onset of menopause.

Conclusions—The onset of menopause is associated with a significant increase in the risk of cardiac events (dominated by recurrent episodes of syncope) in LQT2 women, suggesting that careful follow-up and continued long-term therapy are warranted in this population.

Key Words: estrogen ■ long QT syndrome ■ testosterone ■ women

Congenital long-QT syndrome (LQTS) is the most common inherited arrhythmogenic disorder that predisposes to sudden cardiac death (SCD) in young individuals without structural heart disease.1 Cardiac events in LQTS patients are attributed to episodes of torsades de pointes, believed to be initiated by afterdepolarization events during the prolonged refractory period secondary to a mutation in the affected ion channels.2 We have previously shown that LQTS women experience a significant increase in the risk of cardiac events after the onset of adolescence and during the postpartum period,3–5 with a more pronounced risk increase among carriers of the LQT2 genotype.5,5 Furthermore, female sex was shown to be associated with a longer baseline QTc, and is an independent risk factor for development of torsades de pointes in acquired (drug-induced) LQTS,6–10 suggesting that the effect of sex hormones on arrhythmic risk may be related to cardiac ion channel mechanisms.6,7 Estrogen and progesterone were shown to exert opposite effects on cardiac potassium channel activity.6,12 Thus, LQTS women who harbor mutations that impair the potassium channel may be sensitive to the changes in the levels of sex hormones that occur during the perimenopausal period. Currently, however, there are no data regarding the effect of menopause on the clinical course of women with this inherited cardiac disorder.

Clinical Perspective on p 000

The aims of the present study were to evaluate the effect of menopause on the risk for cardiac events among women with...
genetically confirmed mutations in the \textit{KCNQ1} and \textit{KCNH2} potassium channels and to examine a possible association between treatment with hormonal therapy and the risk of cardiac events in this population.

**Methods**

**Study Population**
The study population was drawn from the US portion of the International LQTS Registry. Women \( \geq 30 \) years of age were included in the study if they had genetically confirmed mutations in the LQT1 and LQT2 genes and had completed a prospectively designed follow-up questionnaire regarding menses, hormonal therapy, and acquired comorbidities (see Data Collection below). The final study sample comprised 282 LQT1 (\( n=151 \)) and LQT2 (\( n=131 \)) women from 104 proband-identified families. The LQTS genotype was determined with standard mutational analytic techniques involving 5 established genetic laboratories associated with the International LQTS Registry.

**Data Collection**
Clinical data were recorded on prospectively designed forms, and included individual and family history and demographic, ECG, therapeutic, and cardiac event information. On enrollment in the registry, a 12-lead ECG was obtained from each subject, as described previously.\(^{13}\) From this first recorded ECG, the duration of the QT interval was assessed from lead II (or lead I or III if the QT interval could not be measured from lead II) and corrected for heart rate (QTc) by use of the Bazett formula.\(^{14}\) Additional serial QTc recordings were obtained from ECGs recorded during follow-up contacts, usually at yearly intervals. Routine clinical and ECG parameters were acquired at the time of enrollment.

All study patients were also prospectively followed up for data regarding non-LQTS comorbidities (shown in Table 1), date of last menstrual period, and use and type of hormonal therapy (ie, estrogen- or progesterone-containing hormonal therapy). Data were collected through a preformed questionnaire sent to enrolled adult subjects at the yearly follow-up assessment.

Subjects provided informed consent agreeing to inclusion in the registry and subsequent genetic and clinical studies. The study was approved by the University of Rochester Medical Center Research Subjects Review Board.

**Definitions**
The age at onset of menopause was defined as 1 year after the reported age of the last menstrual period.\(^{15}\) To evaluate the effect of hormonal status on the risk of cardiac events, follow-up time was prespecified into the following 3 periods based on a model developed at the Stages of Reproductive Aging Workshop:\(^{15}\); (1) the menopause transition period, characterized by variable menstrual cycles and high follicular-stimulating hormone values, most commonly lasting 4 to 5 years\(^{16}\) (defined in the present study as follow-up starting 5 years before the onset of menopause and ending at the age at onset of menopause); (2) the reproductive period, characterized by regular menstrual cycles (defined in the present study as follow-up time beginning at 30 years of age and ending at the onset of the menopausal transition period); and (3) the postmenopausal period (defined in the present study as the 5-year period after the age at onset of menopause). The postmenopausal period was further subdivided by treatment with hormonal therapy during this time period. Because only a minority (2.1%) of study subjects were using a progesterone-containing hormonal regimen, only women who received estrogen therapy were included in this subanalysis.

**Outcome Measures**
To facilitate an evaluation of the effect of the menopausal periods on the risk of recurrent cardiac events, we used statistical methodology that allowed the inclusion of repeated nonfatal syncopal episodes in the multivariate models. Therefore, the primary end point of the present study was the occurrence of recurrent syncopal during follow-up.

Because modeling of recurrent events does not allow inclusion of lethal or near-lethal events, the consistency of the results was also

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LQT1 ( n=151 )</th>
<th>LQT2 ( n=131 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of SCD, n (%)</td>
<td>26 (17)</td>
<td>25 (19)</td>
<td>0.69</td>
</tr>
<tr>
<td>Baseline ECG after 30 y of age (mean±SD), ms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTc</td>
<td>490±49</td>
<td>486±54</td>
<td>0.19</td>
</tr>
<tr>
<td>RR</td>
<td>895±155</td>
<td>940±183</td>
<td>0.05</td>
</tr>
<tr>
<td>QRS</td>
<td>83±13</td>
<td>81±16</td>
<td>0.05</td>
</tr>
<tr>
<td>PR</td>
<td>160±24</td>
<td>156±23</td>
<td>0.18</td>
</tr>
<tr>
<td>LQTS-related therapies, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ß-blockers</td>
<td>85 (56)</td>
<td>89 (68)</td>
<td>0.05</td>
</tr>
<tr>
<td>LCSD</td>
<td>1 (1)</td>
<td>6 (5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>4 (3)</td>
<td>19 (15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICD</td>
<td>23 (15)</td>
<td>33 (25)</td>
<td>0.04</td>
</tr>
<tr>
<td>Menopause data and comorbidities*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopause, n (%)</td>
<td>102 (68)</td>
<td>85 (65)</td>
<td>0.64</td>
</tr>
<tr>
<td>Age at menopause, y</td>
<td>48±6</td>
<td>49±6</td>
<td>0.54</td>
</tr>
<tr>
<td>Estrogen therapy, n (%)</td>
<td>59 (39)</td>
<td>43 (33)</td>
<td>0.28</td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td>7 (5)</td>
<td>5 (4)</td>
<td>0.74</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>4 (3)</td>
<td>0 (0)</td>
<td>0.13</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>0.63</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>65 (43)</td>
<td>42 (32)</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>4 (3)</td>
<td>7 (5)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>23 (15)</td>
<td>13 (10)</td>
<td>0.18</td>
</tr>
<tr>
<td>Asthma, n (%)</td>
<td>16 (11)</td>
<td>10 (8)</td>
<td>0.39</td>
</tr>
<tr>
<td>Emphysema, n (%)</td>
<td>2 (1)</td>
<td>0 (0)</td>
<td>0.50</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>18 (12)</td>
<td>10 (8)</td>
<td>0.23</td>
</tr>
<tr>
<td>CABG, n (%)</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>0.47</td>
</tr>
<tr>
<td>Coronary angiography, n (%)</td>
<td>5 (3)</td>
<td>3 (2)</td>
<td>0.73</td>
</tr>
<tr>
<td>Cardiac events during follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total syncope events, n</td>
<td>63</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>First syncope, n (%)</td>
<td>38 (25)</td>
<td>42 (32)</td>
<td>NA†</td>
</tr>
<tr>
<td>Total syncope events, n</td>
<td>63</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>First syncope, n (%)</td>
<td>38 (25)</td>
<td>42 (32)</td>
<td>NA†</td>
</tr>
<tr>
<td>ACA/SCD, n (%)</td>
<td>11 (7)</td>
<td>11 (8)</td>
<td></td>
</tr>
<tr>
<td>First cardiac event of any type, n (%)‡</td>
<td>46 (30)</td>
<td>51 (39)</td>
<td></td>
</tr>
<tr>
<td>Follow-up time (mean±SD), y</td>
<td>24±6</td>
<td>24±7</td>
<td></td>
</tr>
</tbody>
</table>

SDC indicates sudden cardiac death; LQTS, long-QT syndrome; LCSD, left cervical sympathetic denervation; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting; and ACA, aborted cardiac arrest.

*Data on hormone treatment and age of menopause were obtained from a questionnaire filled out by study subjects.
†Event numbers are presented for descriptive purposes only because a statistical comparison of differences in the crude number of events (that does not take into account the relative time in which the events occurred) has limited interpretability.
‡Comprises the first occurrence of syncope, ACA, or SCD during follow-up (ie, ACA/SCD that occurred after a first syncope was not considered a first event).
assessed by analyzing secondary end points that included the rates of cardiac events of any type (ie, syncope, aborted cardiac arrest [ACA], and SCD), which were adjusted for follow-up during the prespecified perimenopausal periods, and the number of life-threatening cardiac events (comprising ACA or SCD) during the perimenopausal periods.

LQTS-related syncope was defined as a transient loss of consciousness with abrupt onset and offset; ACA was defined as an event requiring defibrillation as part of the resuscitation; and SCD was defined as abrupt in onset without evident cause, if witnessed, or death that was not explained by any other cause if it occurred in a nonwitnessed setting. The circumstances of the events (including data on onset, prodromal symptoms, and seizures) were corroborated by the study coordinators through the patients’ medical files and interviews with individuals about themselves or about family members and categorized by the study specialists using prespecified codes.

**Statistical Analysis**

The clinical characteristics of study subjects were compared between the 2 LQTS genotypes with the χ² test and Fisher exact test for categorical variables and the t test or Mann-Whitney-Wilcoxon test for continuous variables.

To model recurrent syncope over time, a hybridization of the conditional model proposed by Prentice et al 17 combined with Andersen-Gill18 model was used. Complex statistical methodology was used to assess the effect of the menopausal periods on the risk of recurrent cardiac events, because this type of analysis provides important incremental data to sole assessment of crude event rates over those time periods (shown in Figures 1 and 2), including (1) adjustment for important covariates in a multivariate model (such as QTc duration, medical therapy with β-blockers, and acquired comorbidities), thereby facilitating an assessment of the independent effect of each menopause stage on the clinical risk; (2) assessment of the statistical significance of the findings; (3) comparison of risk among women in a similar age range (ie, the Prentice et al–Anderson-Gill model compares the risk of postmenopausal women with that of women in the reproductive period of a similar age, whereas data regarding crude event rates do not take age into account); and (4) incorporation of data regarding the effect of the timing and frequency (intensity) of events during each menopausal stage on clinical risk.

A separate stratum was used for the first and second syncope, as consistent with the conditional approach; subsequent events were modeled with the independence approach of Andersen and Gill. 18 The combined approach was used because of the relatively low number of events after the second syncope stratum, as illustrated by Therneau and Grambsch in similar cases. 19 Prespecified covariates in the multivariate models included the menopausal periods (assessed as time-dependent covariates, with the reproductive period as the reference group for the transition and postmenopausal periods), QTc (assessed from the first ECG recorded after 30 years of age), and β-blocker therapy (modeled as a time-dependent covariate). The results were also validated in an additional analysis that included further adjustment for acquired comorbidities (including diabetes mellitus, smoking status, myocardial infarction, and the presence of angina pectoris, all assessed as time-dependent covariates). Because of the relatively short follow-up time and number of events (n=5) after 52 years of age among women who did not develop menopause by this age (upper quartile of menopause age among study patients), this patient subset was not included in the primary multivariate models. To validate the consistency of our findings across all menopause ages, we carried out a secondary analysis in the total population that was further stratified by the age at onset of menopause (<52 versus ≥52 years).

The risk for recurrent syncope during the postmenopausal period among women who did or did not receive estrogen therapy was evaluated by including postmenopausal estrogen therapy as a time-dependent covariate in the multivariate models. The benefit of β-blocker therapy in reducing the risk of recurrent syncope within each menopausal period was assessed by use of an interaction-term analysis.

The main analyses reported in this study were carried out in separate models for LQT1 and LQT2 women. A total population model, using a menopause period–by-genotype interaction term, was used to assess the difference in menopause-related risk between the 2 genotypes.

The effect of lack of independence, resulting from both multiple events being contributed by subjects and the inherited nature of menopause age, was adjusted for by use of the robust sandwich covariance estimate of Lin and Weil. 19 The statistical software used for the analyses was SAS version 9.20 (SAS Institute Inc, Cary, NC). A 2-sided significance level of 0.05 was used for hypothesis testing.
Table 2. Multivariate Analysis: Effect of Menopause Phase on the Risk of Recurrent Syncope in LQT1 and LQT2 Women*

<table>
<thead>
<tr>
<th>Menopausal Period†</th>
<th>LQT1 Women</th>
<th>LQT2 Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% Confidence Interval)</td>
<td>P</td>
</tr>
<tr>
<td>Menopause transition period vs reproductive period</td>
<td>0.66 (0.19–2.21)</td>
<td>0.50</td>
</tr>
<tr>
<td>Postmenopause period vs reproductive period</td>
<td>0.19 (0.03–1.02)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Multivariate analysis was carried out with combined Prentice et al.17 and Anderson-Gill18 modeling, with the menopausal periods assessed as time-dependent covariates in the multivariate models. Findings are adjusted time-dependent β-blocker therapy and QTc (assessed as a continuous measure). Similar results were obtained in a secondary analysis that included further adjustment for time-dependent comorbidities (including diabetes mellitus, smoking status, prior myocardial infarction, and presence of angina pectoris).

†Menopause transition is defined as the 5-year time period before the reported age at onset of menopause; the postmenopausal period is defined as 5-year time period after the reported age at onset of menopause; the reproductive period is defined as the time period beginning at 30 years of age and ending at the onset of the menopause transition period.

Results

The clinical characteristics of the study subjects by genotype are presented in Table 1. No statistically significant differences between LQT1 and LQT2 women existed regarding baseline QTc, age at onset of menopause, use of estrogen therapy after menopause, or non–LQTS-related comorbidities. Cardiac events during follow-up were dominated by recurrent episodes of syncope (n=150), whereas only 22 study patients (8%) experienced ACA or SCD during follow-up. The overall number of syncope episodes during follow-up was somewhat higher among LQT2 compared with LQT1 women (Table 1).

Menopause Onset and Recurrent Syncope

Multivariate analysis showed that the onset of menopause was associated with a significant increase in the risk of recurrent syncope in LQT2 women (Table 2). Women with the LQT2 genotype had a 3.38-fold (hazard ratio [HR], 3.38; P=0.005) increase in the risk of recurrent syncope during the menopause transition period and an 8-fold (HR, 8.10; P<0.001) risk increase during the postmenopausal period compared with women in the same age group who were in the reproductive period (Table 2). In contrast, among LQT1 women, the risk of recurrent syncope was not significantly changed during the menopause transition period and was reduced (HR, 0.19; P=0.05) after the onset of menopause (Table 2). Notably, interaction-term analysis in a total population model showed a statistically significant difference in the risk related to the onset of menopause between LQT1 and LQT2 women (P=0.02 for postmenopause-by-genotype interaction). Because of the relatively short follow-up time and a corresponding low event rate after 52 years of age among women who did develop menopause by this age, this patient subset was not included in the models of the primary analyses. However, a secondary analysis in the total population that was further stratified by the age at onset of menopause yielded consistent results in both LQT1 women (menopause transition versus reproductive period: HR, 0.82; 95% confidence interval, 0.29 to 2.33; postmenopause versus reproductive period: HR, 0.22; 95% confidence interval, 0.04 to 1.01) and LQT2 women (menopause transition versus reproductive period: HR, 3.45; 95% confidence interval, 1.75 to 6.85; postmenopause versus reproductive period: HR, 5.38; 95% confidence interval, 2.02 to 16.78).

The risk increase associated with the postmenopausal period among LQT2 women was evident among those who either were or were not treated with estrogen therapy (Table 3). Thus, LQT2 women who were not treated with estrogen therapy after menopause experienced nearly an 8-fold (HR, 7.73; P<0.001) increase in the risk of recurrent syncope during the postmenopausal period compared with the reproductive period, and women who received estrogen therapy experienced a >5-fold risk increase (HR, 5.10; P<0.001). In contrast, LQT1 women showed a nonsignificant reduction in the risk of recurrent syncope after the onset of menopause regardless of treatment with estrogen therapy (Table 3).

Time-dependent β-blocker therapy was shown to be associated with a significant reduction in the risk of recurrent syncope among both LQT1 and LQT2 women (HR, 0.40 and 0.51, respectively; P=0.02 for both; Table 3). The benefit of β-blocker therapy in LQT2 women was not significantly different among the reproductive, menopause transition, and postmenopausal periods (P>0.10 for all menopause period–by–β-blocker therapy interactions), suggesting continued efficacy for this mode of medical therapy after the onset of menopause.

Menopause Onset and Cardiac Events of Any Type

Consistent with the results from the multivariate models that assessed the primary end point of recurrent syncope among study patients, analysis of the rate of cardiac events of any type during follow-up (syncope, ACA, or SCD) showed that among LQT2 women the cardiac event rate was lowest during the reproductive period (1.1 per 100 patient-years), intermediate during the menopause transition period (1.7 per 100 patient-years), and highest during the postmenopausal period (3.9 per 100 patients-years), whereas LQT1 women experienced a reduction in event rates after the reproductive period (Figure 1). Furthermore, analysis of the effect of estrogen therapy on the rate of cardiac events (Figure 2) showed that the onset of menopause was associated with an increase in the rate of cardiac events among LQT2 women who did or did not receive estrogen therapy (4.2 and 3.8 events per 100 patient-years, respectively) compared with the
reproductive and menopause transition periods (1.1 and 1.7 events per 100 patient-years, respectively), whereas LQT1 women experienced a reduction in the rate of cardiac events after the onset of menopause regardless of treatment with estrogen therapy (Figure 2).

Menopause Onset and Life-Threatening Cardiac Events

The frequency of life-threatening cardiac events (ACA or SCD) was similar between LQT1 and LQT2 women (Table 1). However, when the number of life-threatening cardiac events related to the onset of menopause, a similar pattern was identified, showing a reduction in the number of life-threatening events among the evaluated time periods in LQT1 patients (5, 4, and 2 events during the reproductive, menopause transition, and postmenopausal periods, respectively) and an increase in LQT2 patients (2, 3, and 6 events during the respective time periods). Because of the relatively small number of life-threatening cardiac events during follow-up (n = 22), this end point was not assessed with multivariate modeling.

Discussion

The present study is the first to assess the clinical course of women with congenital LQTS after the onset of menopause. Our findings suggest several important clinical implications regarding the risk assessment and management of women with this inherited cardiac disorder in the older age group: (1) The perimenopausal period (comprising the 5-year time periods before and after the age at onset of menopause) is associated with a pronounced increase in the risk for recurrent episodes of syncope among women with genetically confirmed LQT2; (2) menopausal status has an opposite effect on the risk of LQT1 women; (3) the effect of menopause on the clinical course of LQTS women is independent of treatment with estrogen therapy; and (4) β-blocker therapy is associated with a significant reduction in the risk of recurrent syncope in this population and should therefore be continued in all women with the LQT2 genotype (without contraindications) even after the onset of menopause. It should be noted that syncope accounted for 85% and 89% of the total number of cardiac events experienced by LQT1 and LQT2 women, respectively, suggesting that the risk related to the onset of menopause is dominated by nonfatal syncopal events.

Effect of Gonadal Hormones on Cardiac Ion Channel Activity Related to Long-QT Syndrome Types 1 and 2

Progesterone and estrogen are lipophilic gonadal steroid hormones with effects that are derived mainly from long-acting transcriptional regulation on nuclear receptors referred to as genomic effects. Progesterone was shown to have a short-acting (ie, nongenomic) effect on shortening the action potential duration and to provide protection against arrhythmias through modulation of slowly activating delayed rectifier potassium currents (IKr) and L-type calcium currents (ICaL) by a pathway that involves progesterone receptors.11 However, studies that examined the genomic effects of progesterone on the cardiac ion channels did not identify a similar long-term effect.20,21 Compared with progesterone, estrogen was shown to exhibit both short-acting (ie, nongenomic) and genomic effects on the IKr channel, including a reduction in channel expression and prolongation of ventricular repolarization,20,21 A large-scale clinical study of postmenopausal women treated with hormone therapy revealed significant QTc prolongation with unopposed estrogen therapy compared with no effect on the QTc interval with combined estrogen-progesterone therapy or with no therapy.22 Notably, recent data suggest that the long-term mechanism related to the effect of estrogen on IKr regulation is receptor independent23,24 and therefore may not fall into the classic definition of “genomic-derived” effect. These long-term estrogen effects provide a possible explanation for the susceptibility of women to drug-induced QT prolongation and arrhythmias25,26

Table 3. Multivariate Analysis: Effect of Therapies During Follow-Up on the Risk of Recurrent Syncope in LQT1 and LQT2 Women*

<table>
<thead>
<tr>
<th>Menopausal Phase†</th>
<th>LQT1 Women</th>
<th>LQT2 Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% Confidence Interval)</td>
<td>P</td>
</tr>
<tr>
<td>Postmenopause vs premenopause risk by treatment with estrogen therapy†</td>
<td>0.20 (0.02–2.08)</td>
<td>0.18</td>
</tr>
<tr>
<td>Postmenopause without estrogen HRT vs reproductive period</td>
<td>0.46 (0.07–3.07)</td>
<td>0.42</td>
</tr>
<tr>
<td>Postmenopause with estrogen HRT vs reproductive period</td>
<td>0.40 (0.17–0.87)</td>
<td>0.02</td>
</tr>
<tr>
<td>β-blocker effect†</td>
<td>0.30 (0.10–0.86)</td>
<td>0.02</td>
</tr>
<tr>
<td>β-blocker vs no β-blocker therapy</td>
<td>0.45 (0.20–0.99)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

HRT indicates hormone replacement therapy.

*Multivariate analysis was carried out with combined Prentice et al17 and Anderson-Gill18 modeling, with the menopausal periods and therapies assessed as time-dependent covariates in the multivariate models. Findings are adjusted time-dependent β-blocker therapy and QTc (assessed as a continuous measure). Similar results were obtained in a secondary analysis that included further adjustment for time-dependent comorbidities (including diabetes mellitus, smoking status, prior myocardial infarction, and presence of angina pectoris).

†Estrogen therapy during the postmenopausal phase was assessed as a time-dependent covariate. The effects of progesterone therapy and of estrogen therapy during the transitional phases were not assessed owing to sample size limitations.
and for the increased risk for cardiac events that occurs in LQT2 women after the onset of adolescence.\textsuperscript{4} Hormonal changes may also explain the increase in the risk that was observed among LQT2 women during the postpartum period\textsuperscript{5}; several studies in which serum measurements of gonadal hormones were obtained at the postpartum era indicate higher estrogen levels in this time period, although this pattern is more evident among lactating mothers.\textsuperscript{27–29}

Testosterone, the male steroid hormone generally derived in women from peripheral intracrine conversion of dehydroepiandrosterone, has also been shown to exert a substantial impact on ventricular repolarization and action potential duration through nontranscriptional modulation of the \( I_{K_{c}} \) channel.\textsuperscript{10,30} Long-term testosterone exposure has been shown to shorten action potential duration and ventricular repolarization in several studies\textsuperscript{31–33} and to diminish the risk of early afterdepolarizations associated with dofetilide treatment in other animal models.\textsuperscript{34} Accordingly, the QTc interval, although similar in male and female children, has been shown to shorten in male subjects after the onset of adolescence while remaining close to its preadolescent value in women.\textsuperscript{35} These androgen-related effects may also explain the higher risk observed among LQT2 women compared with men after the onset of adolescence.\textsuperscript{4}

**Perimenopausal Changes in Gonadal Hormones Levels and the Risk of Cardiac Events in LQT1 and LQT2**

As follicular-stimulating hormone levels start to rise at the 4- to 5-year period before menopause, both estrogen and progesterone levels decline until reaching a minimum after menopause has occurred.\textsuperscript{36} Although estrogen decline is characterized by a fluctuation pattern, with frequent level changes until reaching its nadir, progesterone decline is steadier.\textsuperscript{36} A steady and significant decline also takes place in testosterone and dehydrotestosterone levels during and after menopause, with smaller changes observed after 60 years of age.\textsuperscript{37} After the onset of menopause, adipose tissue becomes quantitatively the most important site of aromatization of androgens to estrogens and thus the main source of extraglandular estrogen synthesis.\textsuperscript{38,39} These adipose tissue–based estrogens were found to correlate with plasma levels in postmenopausal women.\textsuperscript{40} Thus, a new and complex hormonal status quo is established after menopause at which hormonal status is established only by hormonal blood levels, which were not obtained for this study. An increase in the rate of cardiac events after menopause may be related to acquired comorbidities in an older population. To reduce possible age-related bias, we carried out multivariate models that included further adjustments for acquired comorbidities and stratified the analyses by age. Furthermore, menopause-related risk was shown to be significantly different between LQT1 and LQT2 women, suggesting that the association between menopause and the risk of cardiac events among women with LQT2 genotype is independent of an aging effect.

Our findings are also consistent with prior studies that showed an increase in the risk for drug-induced torsade de pointes (mediated through inhibition of the \( I_{K_{c}} \) channel, also affected in the LQT2 syndrome carriers) after the onset of menopause,\textsuperscript{6} further suggesting that changes in sex hormones after the onset of menopause affect arrhythmic risk in LQT2 patients. In contrast, menopause was not associated with an increase in the risk for cardiac events among LQT1 women because carriers of this genotype harbor mutations that affect \( I_{K_{c}} \), whereas the estrogen and diminished testosterone levels in menopause exert their main QT-prolonging effects through suppression of \( I_{K_{c}} \) and loss of \( I_{K_{c}} \) enhancement, respectively.

It is also possible that differences in the risk related to the onset of menopause between LQT1 and LQT2 women may be related to the different mode of onset of torsade de pointes between the 2 genotypes. The onset of arrhythmic events in LQTS was shown to be genotype specific, being predominantly pause dependent in LQT2 and rarely associated with a pause in LQT1.\textsuperscript{41,42} Thus, the possible increased occurrence of ventricular extrasystolic beats (and the associated extrasystolic pauses) during the perimenopausal period is likely to trigger arrhythmias more frequently in LQT2 than in LQT1 women.

**Study Limitations**

Although the onset of menopause is known to be associated with declining estrogen, progesterone, and androgen levels, these levels may fluctuate significantly,\textsuperscript{36,38} and thus the exact hormonal status for each patient could be established only by hormonal blood levels, which were not obtained for this study. An increase in the rate of cardiac events after menopause may be related to acquired comorbidities in an older population. To reduce possible age-related bias, we carried out multivariate models that included further adjustments for acquired comorbidities and stratified the analyses by age. Furthermore, menopause-related risk was shown to be significantly different between LQT1 and LQT2 women, suggesting that the association between menopause and the risk of cardiac events among women with LQT2 genotype is independent of an aging effect.

The primary analysis in the present study focused on the risk for recurrent syncope, which may also include events that are nonarrhythmic in nature. To minimize the bias associated with this limitation, syncopal events were categorized by the study specialists. Thus, nonabrupt events associated with prodromal symptoms of dizziness or lightheadedness (21% of the total events experienced by women during follow-up) and those associated with seizures (4% of the total events experienced by women during follow-up) were not included in the present analysis. Despite this, it is possible that some events assessed in the present study were nonarrhythmic in nature because 33% of neurocardiogenic syncopal events may occur without prodromal symptoms, especially in older adults.\textsuperscript{43} Furthermore, in the older age group, even more severe cardiac events (including ACA or SCD) may not be LQTS-related.\textsuperscript{44} It should be noted, however, that for this end point a similar genotype-specific pattern was identified, showing a reduction in the number of life-threatening events among the evaluated time periods in LQT1 women and an increase in the number of life-threatening events in LQT2 women. Thus, the fact that the 3
end points assessed in the present study (ie, recurrent syncope, cardiac events of any type, and ACA/SCD) consistently showed an opposite genotype-speciﬁc association with menopause strongly suggests that menopause onset affects the risk for arrhythmic events in this population.

Follow-up time after 52 years of age in women who did not experience the onset of menopause by this age was very limited. Therefore, women with a menopause age of ≥52 years were not included in the primary analyses. The consistent results obtained in the secondary total population models suggest that the genotype-speciﬁc effect of menopause on the risk of cardiac events in LQTS patients is independent of age at the onset of menopause.

Conclusions and Clinical Implications

The present study extends prior observations regarding the pivotal effect of sex steroid hormones on the phenotypic expression of LQTS. We have shown that the clinical course of LQTS women during the perimenopausal period is related to the type of the affected cardiac ion channel. Thus, LQT2 women (having mutations that affect $I_{Kr}$) were shown to have a pronounced increase in the risk for recurrent episodes of syncope after the onset of menopause, whereas among LQT1 women (having mutations that affect $I_{Ks}$), the risk of recurrent syncope was reduced during the same time period. These findings suggest that a genotype-speciﬁc approach should be used for risk assessment and management of LQTS women even after the onset of menopause.

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Disclosures

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References

Prior studies have shown that women with congenital long-QT syndrome experience increased risk for cardiac events after the onset of adolescence and during the postpartum period. This risk increase was shown to be more pronounced among women with the LQT2 genotype, suggesting that sex hormones may modify the clinical course of patients with this inherited arrhythmic disorder. The present study is the first to assess the clinical course of long-QT syndrome women after the onset of menopause. We show a genotype-specific association with the risk for cardiac events during the perimenopausal period, including a pronounced increase in the risk for cardiac events (dominated by recurrent episodes of syncope) among LQT2 women and an opposite reduction in the rate of cardiac events in LQT1 women. Notably, the pronounced effect of menopause on the clinical course of long-QT syndrome women was independent of the administration of estrogen therapy. The study also shows that β-blocker therapy is associated with a significant reduction in the risk of recurrent episodes of syncope in long-QT syndrome women during this time period, supporting the continued use of this mode of medical therapy in all women with the LQT2 genotype (without contraindications) even after the onset of menopause. Thus, the present findings suggest that a genotype-specific approach should be used for risk assessment and management of long-QT syndrome women even after the onset of menopause.
Risk of Recurrent Cardiac Events After Onset of Menopause in Women With Congenital Long-QT Syndrome Types 1 and 2

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