Use of oral contraceptives in women with congenital long QT syndrome

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BACKGROUND Use of oral contraceptives (OCs) may modulate the clinical course of women with congenital long QT syndrome (LQTS). The safety of OC use by sex hormone content has not been assessed in women with LQTS.

OBJECTIVE We aimed to evaluate the association of OCs with the risk of cardiac events (CEs) in women with LQTS.

METHODS Beginning in 2010, information on menarche onset, OC use, pregnancy, and menopause were obtained from women enrolled in the Rochester LQTS Registry. Type of OC was categorized as progestin-only, estrogen-only, or combined (estrogen/progestin). Andersen-Gill multivariate modeling was used to evaluate the association of time-dependent OC use with the burden of CE (total number of syncope, aborted cardiac arrest, and LQTS-related sudden cardiac death) from menarche onset through 40 years. Findings were adjusted for genotype, corrected QT duration, and time-dependent β-blocker therapy.

RESULTS A total of 1659 women with LQTS followed through March 2021, of whom 370 (22%) were treated with an OC. During a cumulative follow-up of 35,797 years, there were a total of 2027 CE. Multivariate analysis showed that progestin-only OC was associated with a pronounced 2.8-fold ($P = .01$) increased risk of CEs in women who did not receive β-blocker therapy, while β-blockers were highly protective during progestin-only OC treatment (hazard ratio 0.22; $P = .01$; $P = .006$ for β-blocker-by-OC interaction). The risk associated with OC use without concomitant β-blocker treatment was pronounced in women with LQTS type 2.

CONCLUSION Our findings suggest that progestin-only OC should not be administered in women with LQTS without concomitant β-blocker therapy. OCs should be used with caution in women with LQTS type 2.

KEYWORDS β-Blockers; Long QT syndrome; Oral contraceptives; Sudden cardiac death; Syncope; Women

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Introduction

Long QT syndrome (LQTS) is an arrhythmogenic genetic disorder characterized by prolonged ventricular repolarization and is commonly associated with cardiac events (CEs) such as syncope, cardiac arrest, and sudden cardiac death.[1,2] Prior studies have shown that women experience an increased risk of CEs after the onset of adolescence,[3–5] during the postpartum period,[6,7] and during the perimenopause period[8]; just importantly, the increase in CE risk during the postpartum and perimenopause period was shown to be more pronounced in women with the LQTS type 2 (LQT2) genotype.[6–8] In contrast to women with LQTS, the risk of CE in men is attenuated after the onset of adolescence.[3–5] The mechanisms underlying this sex difference are related to the modulating effects of sex hormones on the potassium channels associated with this inherited genetic disorder. Estrogen and progesterone were shown to have varying effects on IKs (Kv7.1) and IKr (Kv11.1) currents,[9] whereas testosterone increases the potassium channel currents, resulting in a shorter

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corrected QT (QTc) duration in both animal and human studies.[9]

The use of oral contraceptive (OC) medications represents a therapeutic model with high content of sex hormones, relating to the proportion of progesterone and estrogen in each formulation. In addition, specific progestin OC formulations exhibit variable androgenic and antiandrogenic activity.

We hypothesized that different OC formulations (categorized broadly as progestin-only, estrogen-only, or combined [estrogen/progestin]) may confer a different CE risk in LQTS and that the risk may, in turn, be modified by β-blocker treatment. Accordingly, in the present study we aimed to (1) evaluate the association of the 3 main OC formulation types with the risk of CE in women with LQTS, (2) determine the effect of β-blocker therapy on the CE burden during OC use, and (3) assess the association of OC use with CE risk by genotype.

Methods

Study population

This study included patients from the Rochester LQTS Registry. Beginning in September 2010, information on menstruation, OC use, pregnancy, and menopause were requested from all women in the LQTS registry. Data were updated from registry women on a yearly basis. Questionnaires capturing this information were sent out to female patients in the registry who met the following criteria: (1) genotype positive for LQTS or a QTc interval of $\geq$450 ms and were identified clinically as having LQTS, (2) age $\geq$ 18 years, and (3) alive and gave consent to the study. The total number of patients who have completed the questionnaire through March 2021 was 1656, who comprised the present study population.

This study was approved by the University of Rochester Medical Center Research Subjects Review Board. The research reported in this article adhered to Helsinki Declaration as revised in 2013 guidelines.

Data collection and management

For each patient, information on personal history, including CE, electrocardiograms (ECGs), and therapies, as well as family history was obtained at enrollment. Clinical data were then prospectively collected yearly, which included demographic characteristics, personal and family medical history, ECG findings, medical therapies, left cardiac sympathetic denervation, implantation of a pacemaker or an implantable cardioverter-defibrillator (ICD), and the occurrence of LQTS-related CE. The QT interval was corrected for heart rate by using the Bazett formula to derive the patient's QTc value from the first recorded ECG.[10] The routine approach to QTc assessment in both registries was based on a paper copy of the baseline ECG. Lead II is reported using manual measurements from the onset of the QRS complex to the nadir between the T wave and the isoelectric line or between the T wave and the U wave, if present. Lead V_5 is used as an alternative when QT measurement cannot be done in lead II.

LQTS mutations were identified with the use of standard genetic tests conducted in academic molecular genetics laboratories including Functional Genomics Center, University of Rochester, Rochester, NY; Baylor College of Medicine, Houston, TX; and Boston Children's Hospital, Boston, MA.

Time origin and follow-up

The time origin was selected as the date of menarche to restrict CE counts to a time period when OC use was a likely possibility and to preclude controls (ie, patients who were not taking OCs) coming from premenarche time periods. Follow-up time during pregnancy periods was excluded by temporarily removing pregnant patients from the risk set. This was done because typically OCs are not administered during known pregnancy and because pregnancy itself can confound the occurrence of CE, which tend to be lower during such periods.[6] Follow-up was censored at the age of 40 years to help minimize the confounding effects of perimenopause and postmenopausal periods as well as those arising from other cardiovascular diseases associated with advancing age.

End points

The primary study outcome was the incidence of a first CE after menarche and recurrent CE (defined as syncope, aborted cardiac arrest requiring defibrillation as part of resuscitation, or LQTS-related sudden cardiac death [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 such as sleep]). A secondary outcome was the time of the first occurrence of CE. Syncope as a clinical end point in the registry is adjudicated as a history strongly suggestive of an arrhythmic origin by review of patient data.

Statistical analysis

We compared the clinical characteristics of study patients by treatment with an OC at any time during follow-up by using the Wilcoxon test for continuous variables and the χ^2 test for categorical variables. Categorical data are summarized as frequency (percentage). Continuous data are summarized as mean $\pm$ SD.

Time-dependent multivariate Cox proportional hazards regression analysis was used to identify and evaluate the association of each OC type and the risk of a first CE. All models were further adjusted for QTc duration, genotype, and β-blocker therapy.

The mean cumulative event rate was presented using the Ghosh-Lin curves to display the mean number of recurrent events per patient as appropriate by each OC formulation type, with follow-up starting at the time of OC initiation. The Andersen-Gill non–gap-time model was used to estimate the hazard ratios (HRs) for recurrent CE, allowing for time-dependent strata with separate nonparametric baseline hazard functions for each recurrent event. OC use was modeled as a time-dependent variable to account for the changing status of

Table 1 Baseline clinical characteristics by OC use

Characteristic	No OC (n = 1289)	OC (n = 370)	*P*
Age at diagnosis (y)	19 ± 13	18 ± 11	.03
Follow-up duration (y)	21.9 ± 7.4	21.5 ± 7.0	.74
Proband	400 (31)	122 (33)	.54
Female specific			
Menarche age (y)	12.3 ± 1.6	12.3 ± 1.7	.58
Pregnancy	941 (73)	252 (68)	.07
Menopause	27(2)	30(8)	<.001
First OC type			
Estrogen-only	NA	77 (21)	NA
Progestin-only	NA	81 (22)	NA
Combined	NA	212 (57)	NA
Electrocardiographic*			
QRS interval (ms)	820 ± 160	790 ± 140	.01
RR interval (ms)	856 ± 192	807 ± 213	<.001
QTc interval (ms)	495 ± 50	491 ± 53	.03
Genotype (excluding multiple mutations)			
LQT1	317 (39)	120 (40)	.63
LQT2	273 (33)	109 (37)	.31
LQT3	106 (13)	17 (6)	<.001
LQTS-related therapies during follow-up			
β-Blockers	515 (40)	294 (79)	<.001
Sodium channel blockers	35 (3)	14 (4)	.28
Left cardiac sympathetic denervation	21 (2)	7 (2)	.729
ICD	195 (15)	130 (35)	<.001

Values are presented as mean ± SD or n (%).

ICD = implantable cardioverter-defibrillator; LQT1, 2, 3 = long QT syndrome type 1, 2, 3; LQTS = long QT syndrome; NA = not applicable; OC = oral contraceptive.

*Obtained from the baseline (first) electrocardiogram recorded in the registry.

OC use (being on to going off, and vice versa, or switch to a different OC formulation). The HR was further adjusted for baseline QT interval corrected for heart rate and genotype. Interaction term analysis was used to assess the risk of recurrent CE by OC use with and without concomitant time-dependent β-blocker therapy. In a secondary analysis, we also assessed the possible interactions of OC use by genotype and QTc duration.

Counts of events per 100 patient-years of risk were computed for each OC formulation type. Arrhythmic events were counted in the OC group only if patients were taking OCs at the time of the event. These are crude composite descriptive measures of risk; no statistical tests were conducted.

All tests of significance were 2-tailed with a *P* value of <.05 accepted to indicate statistical significance. Analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Clinical characteristics

Of the 1659 women with LQTS, 370 (22%) were treated with an OC at any time during follow-up. Of the 370 women who were prescribed an OC, 212 (57%) received combined OC, 77 (21%) estrogen-only OC, and 81 (22%) received progestin-only OC. Women in the no OC group were not using other hormone-based contraceptive (ie, injections or intrauterine devices).

The baseline clinical characteristics of study patients by use of OC at any time during follow-up are provided in Table 1. The mean age of menarche was 12.3 years and was not significantly different between the 2 groups. A similar proportion of women experienced pregnancy during follow-up in both groups (in total 72%). The mean QTc duration was somewhat longer in the no OC group than in the OC group (495 ms vs 491 ms, respectively). The distribution of LQTS genotype was also similar between the 2 groups. Among study patients, 26% were genotyped as LQT1 (N = 431), 23% as LQT2 (N = 381), and 7% as LQT3 (N = 116). The proportion of women who received medical therapy with β-blockers and an ICD was significantly higher in the OC group than in the no OC group (Table 1). However, in women prescribed an OC, the rate of β-blocker therapy was similar by formulation type (combined OC 79%; estrogen-only OC 80%; progestin-only 77%).

Risk of CE by OC formulation type

In the total group of 1659 patients, a first CE after menarche onset occurred in 687 women with LQTS (41%), of whom 381 (55%) experienced syncope, 133 (19%) had an aborted cardiac arrest event, 97 (14%) received appropriate ICD shocks, and 76 (11%) had LQTS-related death as a first clinical manifestation.

Multivariate Cox proportional hazards regression modeling for the end point of a first CE consistently showed that treatment with progestin-only OC was associated with a

Table 2 Multivariate analysis: Risk factors for a first CE by type of OC*†

Variable	HR	95% CI	*P*
OC formulation type			
Progestin-only OC vs no OC	2.54	1.09–5.91	.03
Estrogen-only OC vs no OC	0.97	0.23–4.06	.96
Combined OC vs no OC	1.30	0.90–1.88	.17
QTc interval ≥ 500 ms	1.70	1.40–2.06	<.001
Genotype			
LQT2 vs LQT1	1.71	1.38–2.15	<.001
LQT3 vs LQT1	0.89	0.64–1.25	.50
Nongenotyped vs LQT1	1.45	1.18–1.79	<.001
Nongenotyped vs LQT2	0.75	0.61–0.92	.005
β-Blocker therapy	0.66	0.51–0.86	.002

CE = cardiac event; CI = confidence interval; HR = hazard ratio; LQT1, 2, 3 = long QT syndrome type 1, 2, 3; OC = oral contraceptive; QTc = corrected QT.

*All variables are derived from a multivariate adjusted model.

†Similar results were obtained when model was further adjusted for proband status.

statistically significant 2.5-fold increased risk of a first CE as compared with no OC treatment whereas estrogen-only and combined OC were not associated with a significant risk increase (Table 2).

Additional covariates associated with a higher risk of a first CE in the multivariate model included baseline QTc interval ≥ 500 ms (obtained from the first recorded ECG) and the LQT2 genotype (both associated with a ≥70 increase in the risk of a first CE). β-Blocker therapy was associated with an overall 41% reduction in the risk of a first CE (Table 2). Consistent results were shown in a secondary analysis, in which the multivariate model was further adjusted for proband status.

OC formulation type and CE burden with and without concomitant β-blocker therapy

During a cumulative follow-up of 35,797 years, there were a total of 2027 CE in all study patients. The mean cumulative CE rates by OC formulation type are presented in Figure 1. This analysis showed that at 25 years of follow-up after the initiation of each OC type, the mean cumulative rates were highest in women who were prescribed a progestin-only OC (average 1.7 events/y), intermediate in women who were prescribed a combined OC (average 1.2 events/y), and lowest in women who were prescribed an estrogen-only OC (average 0.28 events/y) ($P < .001$ for the overall difference during follow-up).

We subsequently used Andersen-Gill modeling to identify the risk of recurrent CE in women who did and did not receive concomitant β-blocker therapy during OC use (Table 3). This analysis showed that in women who did not receive concomitant β-blocker therapy, progestin-only OC use was associated with a significant 2.8-fold ($P = .01$) increased risk of recurrent CE compared with no OC. In contrast, in women who were treated with β-blockers, the use of progestin-only OC vs no OC was not associated with a significant risk increase (HR 0.54; $P = .19$; $P = .006$ for progestin-only OC-by-β-blocker interaction) (Table 3). Accordingly, β-blocker therapy was associated with a pronounced 78% reduction in the risk of recurrent CE in women with LQTS who were prescribed a progestin-only OC (HR 0.22; 95% confidence interval 0.07–0.74; $P = .01$).

The use of estrogen-only OC vs no OC was not associated with a significant increase in the risk of recurrent CE without or with concomitant β-blocker therapy (HR 0.89 [$P = .70$] and 0.99 [$P = .98$], respectively) (Table 3). Similarly, the use of combined OC was not associated with a significant increase in the risk of recurrent CE with or without

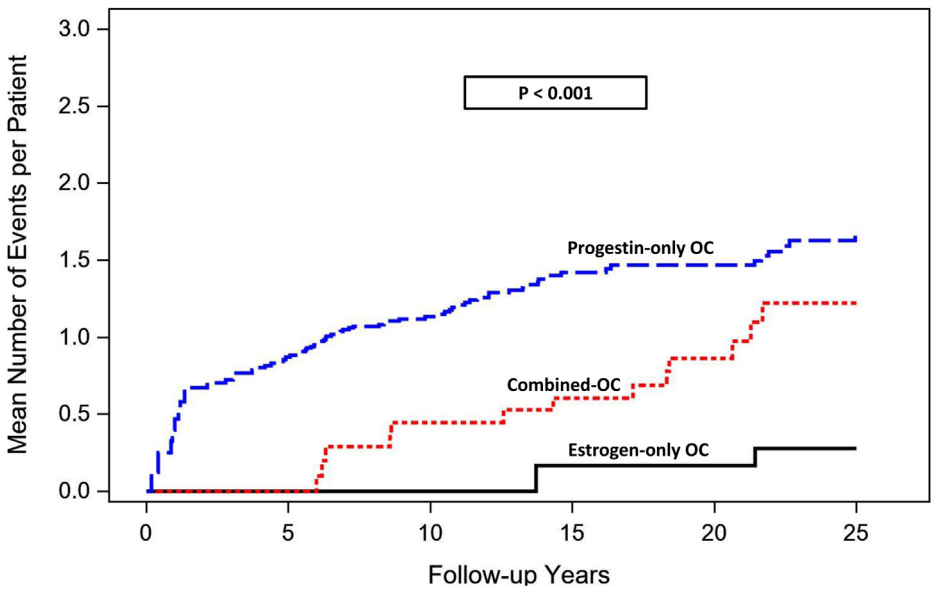

Figure 1 Mean cumulative rate of cardiac event by the type of oral contraceptive (OC) formulation. Curves are displayed using the Ghosh-Lin methodology; follow-up starting at the time of OC initiation.

Table 3 Multivariate analysis: Risk factors for recurrent CE by type of OC with and without β-blocker therapy in the total study population*

Variable	HR	95% CI	*P*	*P* for the interaction
Progestin-only OC vs no OC				
No β-blocker therapy	2.86	1.26–6.54	.01	.006
On β-blocker therapy	0.54	0.49–1.14	.19	
Estrogen-only OC vs no OC				
No β-blocker therapy	0.99	0.36–2.70	.98	.90
On β-blocker therapy	0.89	0.22–3.58	.69	
Combined OC vs no OC				
No β-blocker therapy	1.29	0.87–1.91	.21	.048
On β-blocker therapy	0.74	0.49–1.14	.17	

CE = cardiac event; CI = confidence interval; HR = hazard ratio; OC = oral contraceptive.
*All findings are further adjusted for corrected QT duration and genotype.

concomitant β-blocker therapy (HR 0.74 [$P = .17$] and 1.29 [$P = .21$], respectively) (Table 3). Of note, the difference in risk among combined OC users between on and off β-blockers was marginally statistically significant ($P = .048$ for combined OC-by-β-blocker interaction), suggesting a possible increased risk of combined OC use without concomitant β-blocker therapy.

Assessment of event rates during OC use (Figure 2) consistently showed that in women who did not receive treatment with β-blockers, progestin-only OC was associated with the highest burden of CE (14.1 events per 100 patient-years) as compared with estrogen-only OC (6.2 events per 100 patient-years), combined OC (7.5 events per 100 patient-years), and no OC (7 events per 100 patient-years) (Figure 2A). In contrast, in women who were treated with β-blockers, progestin-only use was associated with a lower CE burden (3.4 events per 100 patient-years) as compared with estrogen-only OC, combined OC, and no OC (4.5, 5.5, and 5.4 events per 100 patient-years, respectively) (Figure 2B).

OC use and CE burden in women with LQT2

We further used Andersen-Gill modeling to identify the risk of recurrent CE by genotype. This analysis showed that women with LQT2 experienced the most pronounced risk associated with OC use. In women with LQT2, progestin-only OC without concomitant β-blocker treatment was associated with an 8-fold ($P < .001$) increased risk of recurrent CE and estrogen-only OC was associated with a corresponding 10-fold ($P = .001$) risk increase (Table 4). Of note, in women with LQT2, interactions for all OC formulation types by β-blocker treatment were statistically significant (Table 4). No other statistically significant interactions of OC use were identified by genotype (LQT1, LQT3, and nongenotyped) or by QTc duration.

Discussion

To our knowledge, this is the first study to assess the association of OC by formulation type with the risk of CE in women with congenital LQTS. We have shown that (1) progestin-only OC therapy confers increased risk of CE in women with LQTS, (2) concomitant β-blocker therapy significantly attenuates the risk of CE during progestin-only OC use, and finally, (3) the risk associated with OC use is most pronounced in women with the LQT2 genotype. These findings suggest that progestin-only OC should not be administered in women with congenital LQTS without concomitant β-blocker therapy and that caution should be exercised when prescribing an OC to women with LQT2.

OC therapy provides women with a reliable method of contraception and are also used for the treatment of abnormal uterine bleeding,[11,12] premenstrual syndrome,[13,14] premenstrual dysphoric disorder,[15] and other conditions.[16] The currently available OC vary in composition from estrogen only, progestin only, and a combination of both estrogen and progestin.[17] Progestins are subdivided into 1 of 4 generations on the basis of when the compound was made available for clinical use, and it has been shown that third- and fourth-generation progestins are better tolerated (including a good parallel treatment of premenstrual dysphoric disorder and moderate acne) than earlier generations. Furthermore, the newer-generation progestins, such as drospirenone, are known to have antiandrogenic effects.[18]

The impact of sex hormones on ventricular repolarization in healthy individuals[19] and those receiving antiarrhythmic drugs[20] have previously been reported, but to date there has not been a thorough investigation evaluating the effect of formulation-specific OC therapy in women with LQTS. Our findings have important implications with regard to the selection of OC therapy in women with LQTS, with strong evidence that progestin-only OC significantly increases the risk of CEs. If in such patients progestin-only OC therapy is deemed necessary (eg, in women in whom estrogen therapy is contraindicated because of a previous venous thromboembolic event or stroke), then β-blocker treatment should be highly encouraged.

The exact mechanism through which progestin-only OC increases the risk of CE remains elusive. Studies evaluating the effects of sex hormones on cardiac depolarization and repolarization during the regular menstrual cycle in women have shown that progesterone is normally associated with effects on ion channels that lead to QT shortening whereas estrogen has the opposite effects, usually resulting in QT

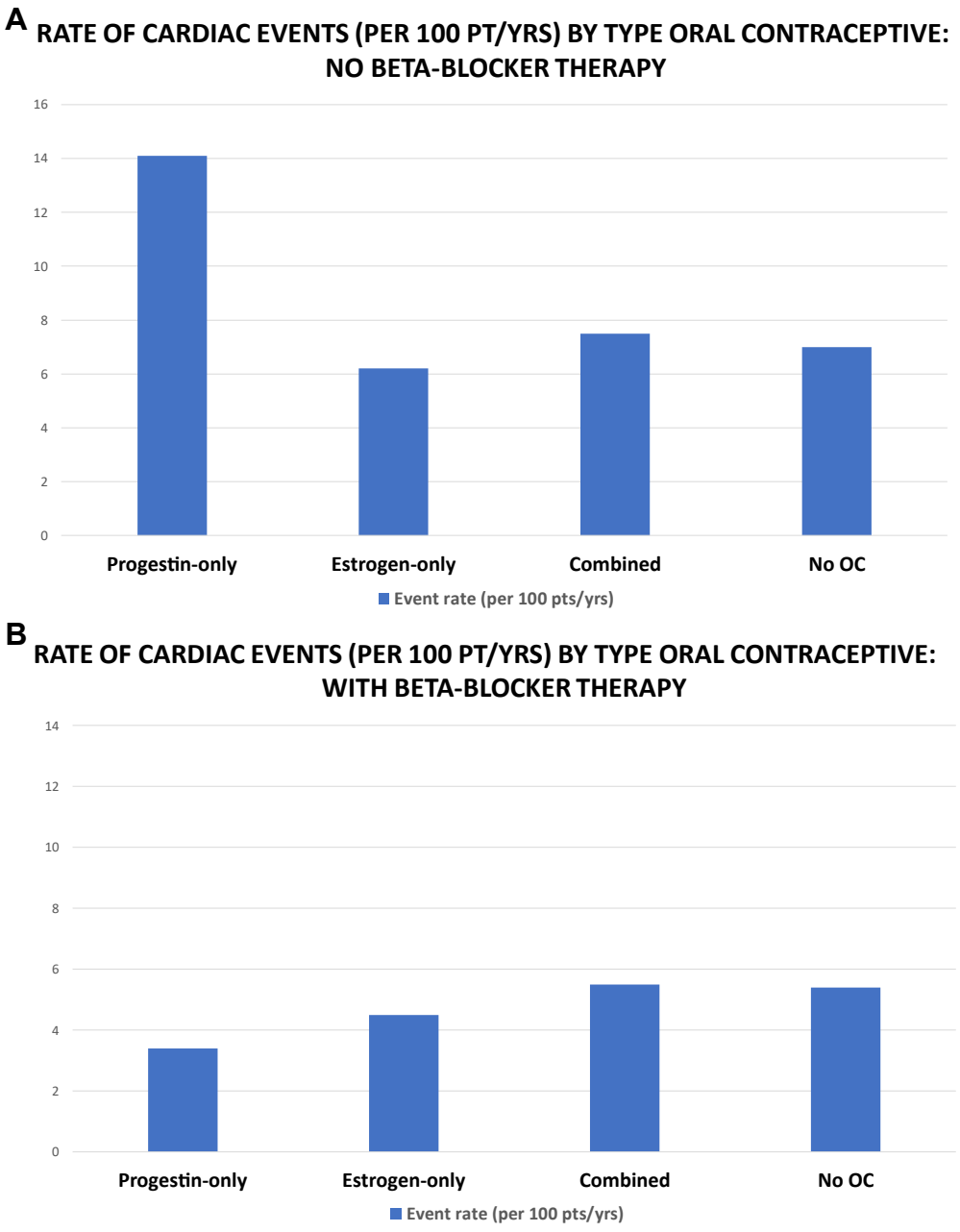

Figure 2 Event rates (per 100 patient-years) by oral contraceptive (OC) formulation type (**A**) without and (**B**) with concomitant β-blocker therapy.

prolongation.[9,21] There are several putative mechanisms for the observed finding of the increased risk of CEs with progestin-only OC therapy in women with LQTS. The degree to which an OC exerts androgenic vs antiandrogenic effects appears to be an important factor that modulates cardiac repolarization.[9] In a study of 34,676 women on OC therapy, those who were on first- and second-generation progestins had a significantly shorter QTc interval than did nonusers ($P < .001$) and, conversely, women taking fourth-generation progestin containing an OC had a significantly longer QTc interval than did nonusers ($P < .001$).[22] Similarly, in another study of patients treated with drospirenone (fourth-generation progestin), the addition of sotalol was associated with significant QTc prolongation whereas the addition of sotalol to levonorgestrel (second-generation progestin) was not associated with QTc prolongation.[23] Of note, in the present study cohort, fourth-generation drospirenone was administered to 53 women, comprising 65% of progestin-only OC. It should also be noted that there are nongenomic effects of OC therapy on cardiac repolarization, through activation of endothelial nitric oxide pathways,[24] that may provide another possible mechanism related to the effect of OC use in LQTS.

Our group previously evaluated the effect of OCs in a smaller cohort of women with LQTS and showed no increase in the risk of CEs when compared with those not using OC.[25] However, an analysis based on the formulation of the OC used was not performed in that study that comprised a relatively small sample (N = 175). The present study, which

Table 4 Multivariate analysis: Risk factors for recurrent CE by type of OC with and without β-blocker therapy in women with LQT2*

Variable	HR	95% CI	*P*	*P* for the interaction
Progestin-only OC vs no OC				
No β-blocker therapy	8.03	4.22–15.29	<.001	.002
On β-blocker therapy	0.42	0.49–1.14	.29	
Estrogen-only OC vs no OC				
No β-blocker therapy	10.05	2.60–38.89	.001	.008
On β-blocker therapy	0.38	0.06–2.66	.33	
Combined OC vs no OC				
No β-blocker therapy	1.51	0.78–2.93	.23	.037
On β-blocker therapy	0.59	0.30–1.15	.12	

CE = cardiac event; CI = confidence interval; HR = hazard ratio; LQT2 = long QT syndrome type 2; OC = oral contraceptive.
*All findings are further adjusted for corrected QT duration.

includes more than 1600 women with LQTS, of whom 360 were on OC, provides additional information on CEs on the basis of the different formulations of OC therapy. Twenty-two percent of patients in our study received progestin-only OC.

We have previously shown that CE risk during the postpartum and perimenopause period is pronounced in women with the LQT2 genotype.[6–8] In the present study, we extend these findings and show a powerful association of all OC formulation types with CE risk in women with LQT2. These findings may be due to the modulating effects of sex hormone on IKr (Kv11.1) currents.[9] Of note, these findings may also have implications for drug-induced LQTS that similarly affects the IKr channel.

Limitations

There are several limitations of our study that require recognition. First, the OC group appears to be a more severely affected group of patients than does the no OC group (Table 1). Thus, it is possible that the relatively high rate of more pronounced phenotypes may have resulted in an overestimation of the effect of OC for the total group and in the marked reduction in CE rate associated with β-blocker therapy in the progestin-only group. It is also possible that more severely affected women with LQTS were more likely to be prescribed an OC to avoid the risks associated with pregnancy, resulting in greater contact with medical care and increased number of medical and device interventions. Second, it should be noted that QTc is influenced by age with a different effect by genotype. However, in the present study the models included only baseline QTc as a risk factor and did not incorporate QTc as a time-dependent measure. Third, it should be noted that it is possible that a subset of women with LQTS were not prescribed β-blockers while on OC due to the fact that they were still not diagnosed with LQTS at the time of OC use. This may also lead to a recall bias of arrhythmic events before LQTS diagnosis. Finally, we have identified that the association of OC use with CE risk is significantly more pronounced in women with LQT2 (N = 382). However, because of sample size limitations, the findings of this subgroup analysis should be further validated in future studies.

Conclusion

Given the results of our study, women with LQTS who are treated with progestin-only OC may need to be offered OC with alternative formulations or should be initiated (or continued) on β-blocker therapy. Our data also suggest that caution should be exercised when prescribing any OC to women with LQT2.

The impact of OC on the wider population of patients with drug-induced LQTS and whether certain formulations of OC may lead to proarrhythmia remains unknown. Prospective studies are needed to further elucidate the mechanisms associated with OC-related arrhythmic risk in patients with congenital and drug-induced LQTS.

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