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Difference in the phenotype among age and sex in inherited arrhythmias

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Korean Heart Rhythm Society
COI Disclosure

Naokata Sumitomo:

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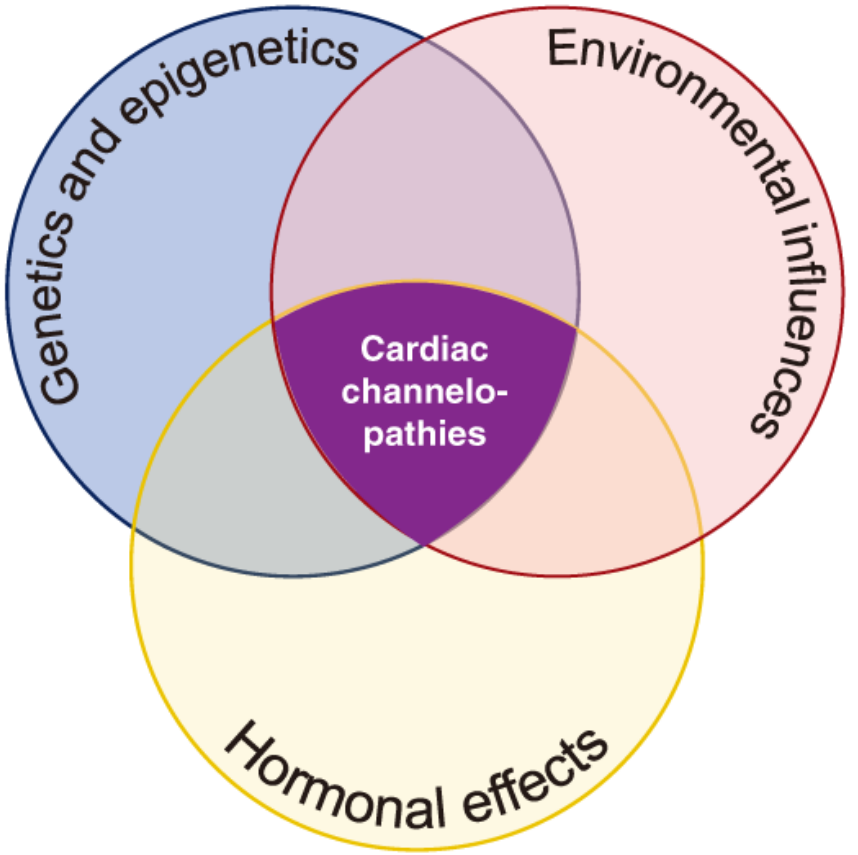
Inherited arrhythmias ≈ Cardiac channelopathies

- 10% of all **sudden cardiac deaths**, most of which occur in individuals **<40 years of age**.
- Inherited in an **autosomal dominant** manner; first-degree family members have a 50% chance of inheriting.
- **Incomplete penetrance** and variable expressivity.
- A wide array of **genetic**, **posttranslational**, and **environmental factors** that influence the cardiac channelopathy phenotype.
- Multifaceted effects of **sex hormones** on cardiac ion channels.
- Men and women with certain cardiac channelopathies show differences in the **age-related penetrance**, disease **expression**, and **risk for SCD**.



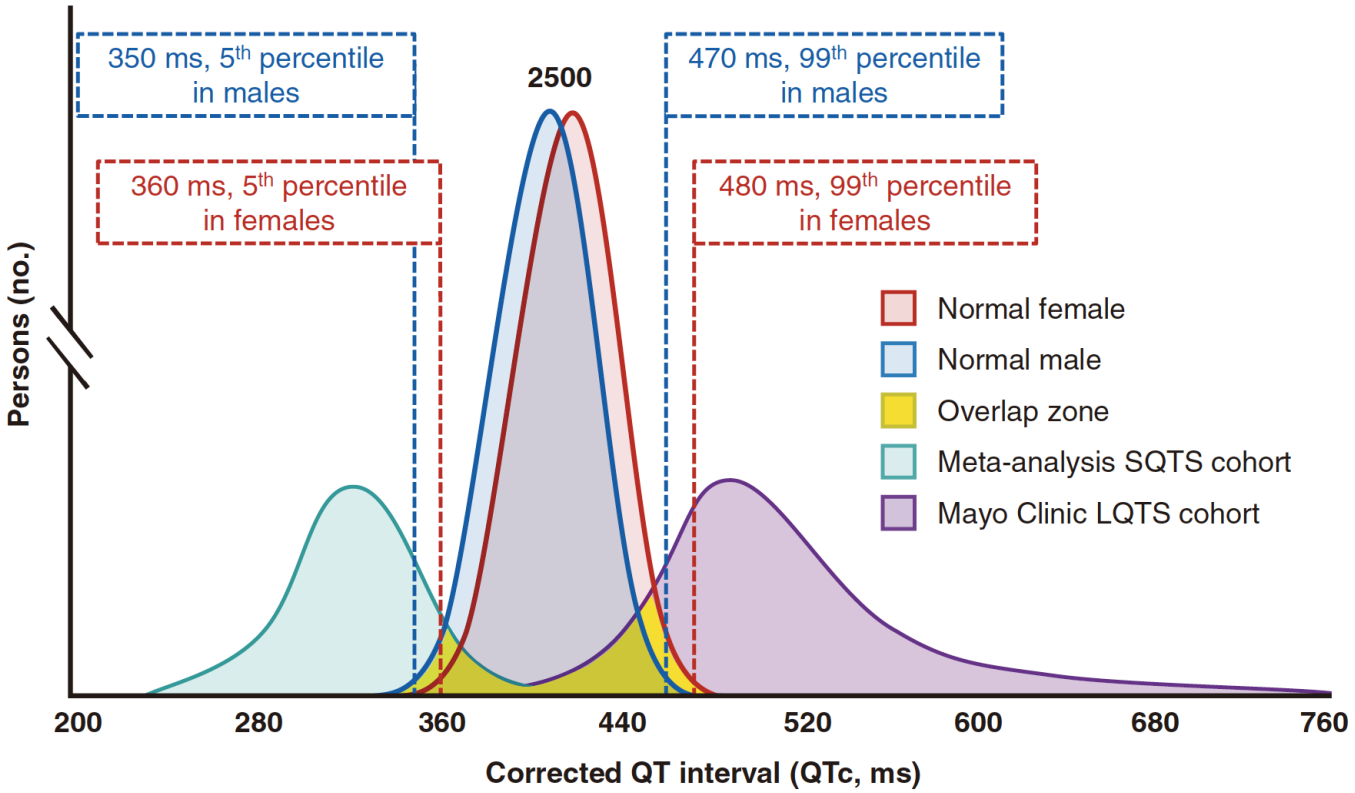
Asatryan B, et al. Circulation. 2021;143:739-752.

Inherited arrhythmia

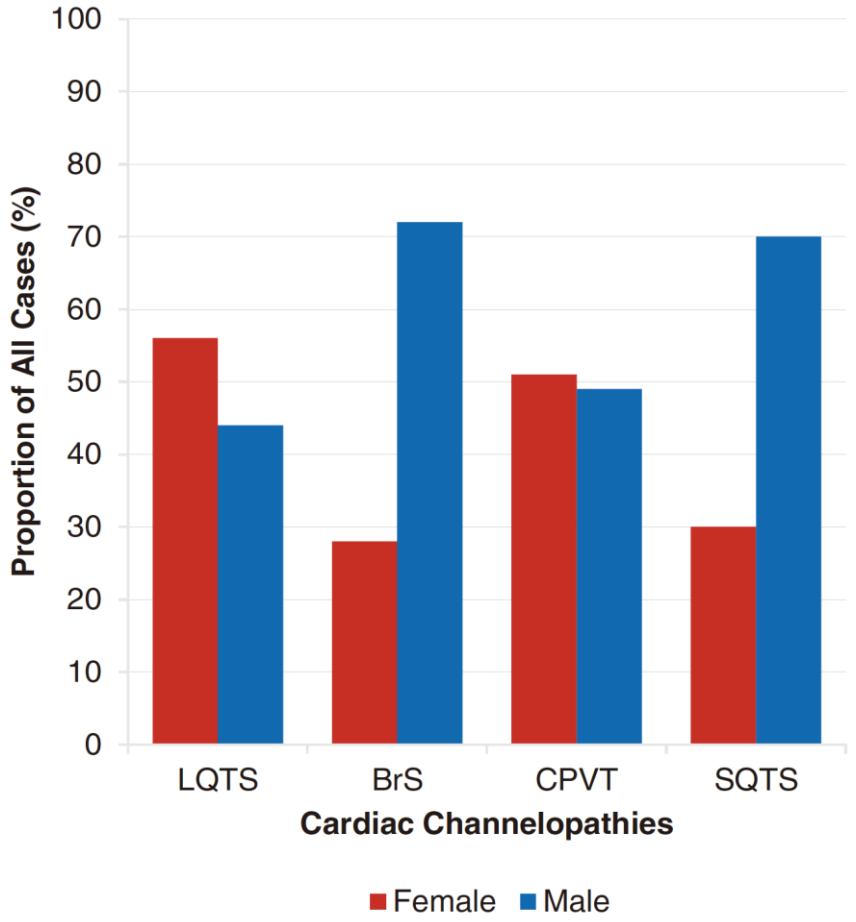
1. Long QT syndrome (LQTS)
    1. Congenital
    2. Acquired
2. Brugada syndrome (BrS)
3. Catecholaminergic polymorphic ventricular tachycardia (CPVT)
4. Short QT syndrome (SQTS)
5. Early repolarization syndrome (ERS, J wave syndrome)
6. Progressive cardiac conduction disturbance (PCCD, Lenegre disease)
7. Familial bradycardia syndrome (sick sinus syndrome, AV block)
8. Arrhythmogenic right ventricular cardiomyopathy (ARVC/D)
9. Dilated cardiomyopathy with bradycardia (Laminopathy)

Sex-Related Differences in Cardiac Channelopathies

Heart rate–corrected QT interval distribution in health and disease



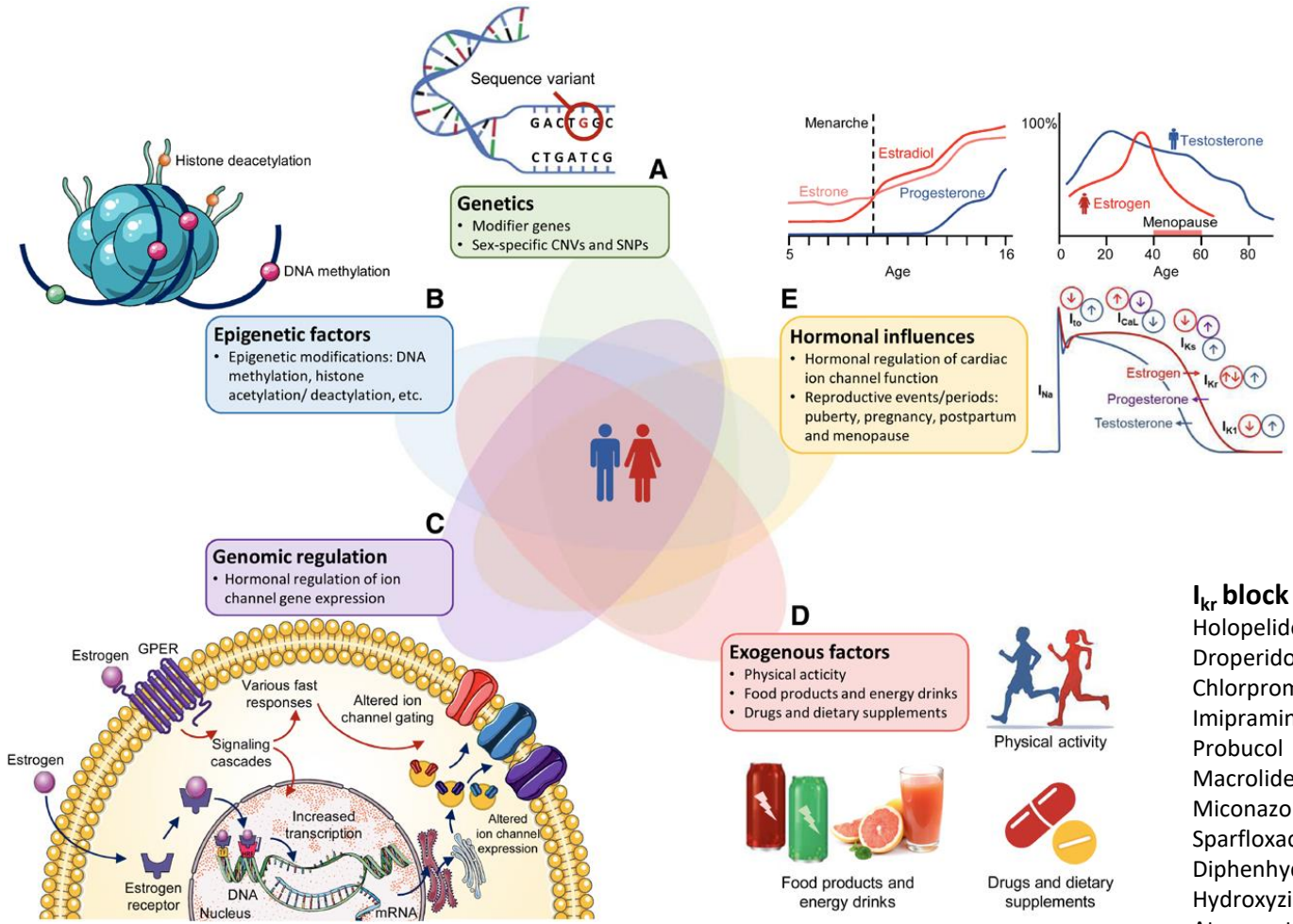
Approximate sex distribution of patients diagnosed with cardiac channelopathies



Asatryan B, et al. Circulation. 2021;143:739–752.

Sex-Related Differences in Cardiac Channelopathies

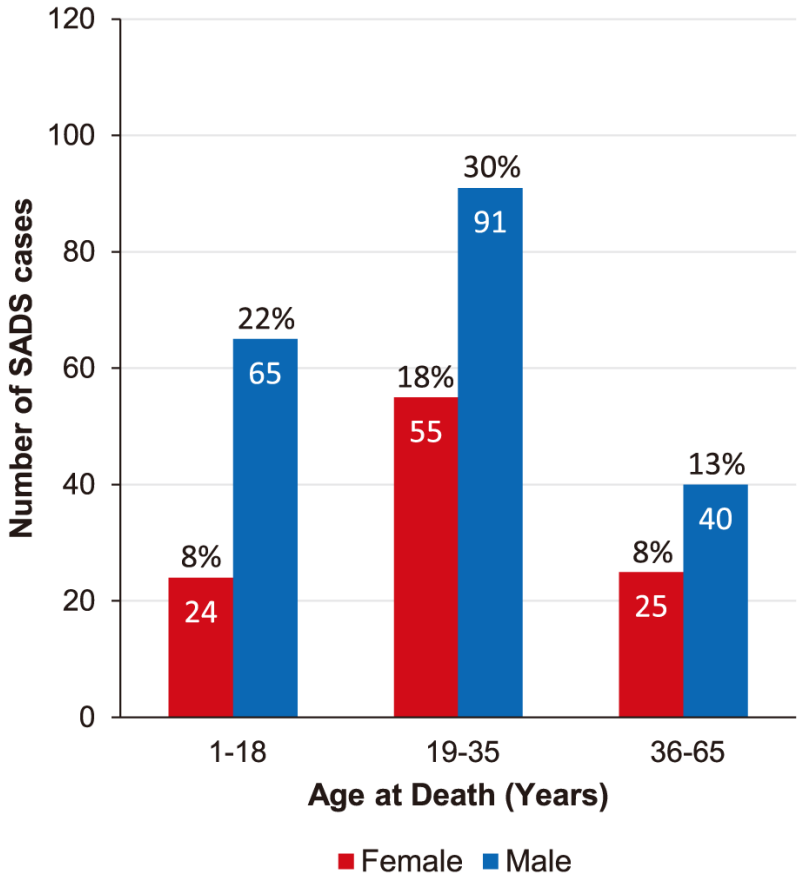
Schematic representation of the complex interplay of factors that determine the sex-related differences in cardiac channelopathies



I_{kr} block
Holopelidol
Droperidol
Chlorpromazine
Imipramine
Probucol
Macrolide
Miconazole
Sparfloxacin
Diphenhydramine
Hydroxyzine
Atomoxetine (Strattera)
Methylphenidate (Consata)

SNPs = single-nucleotide polymorphisms; CNVs = copy number variants; GPER = G-protein–coupled estrogen receptor

Distribution of 302 cases of SADS among age groups in men and women



Asatryan B, et al. Circulation. 2021;143:739–752.

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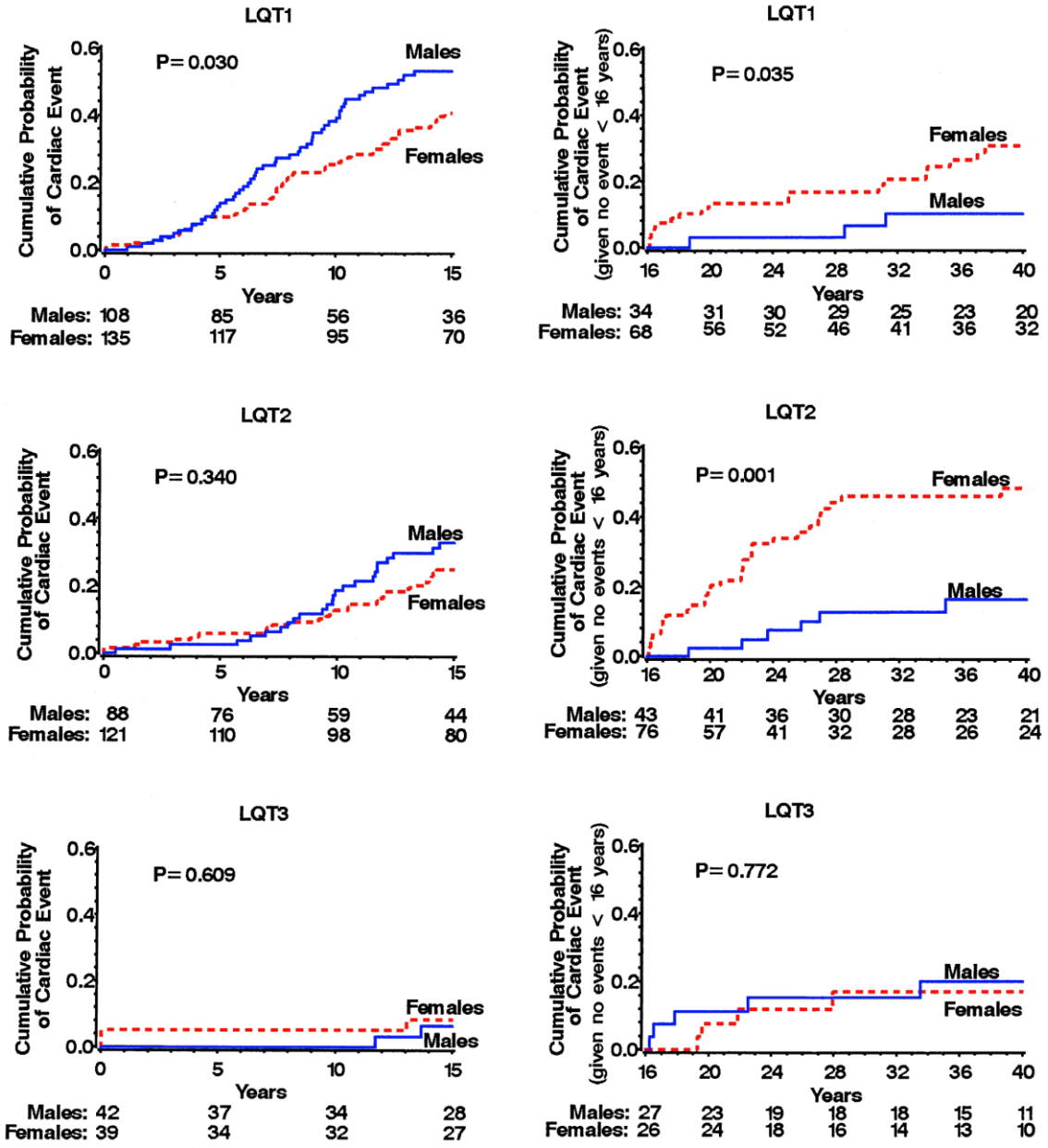
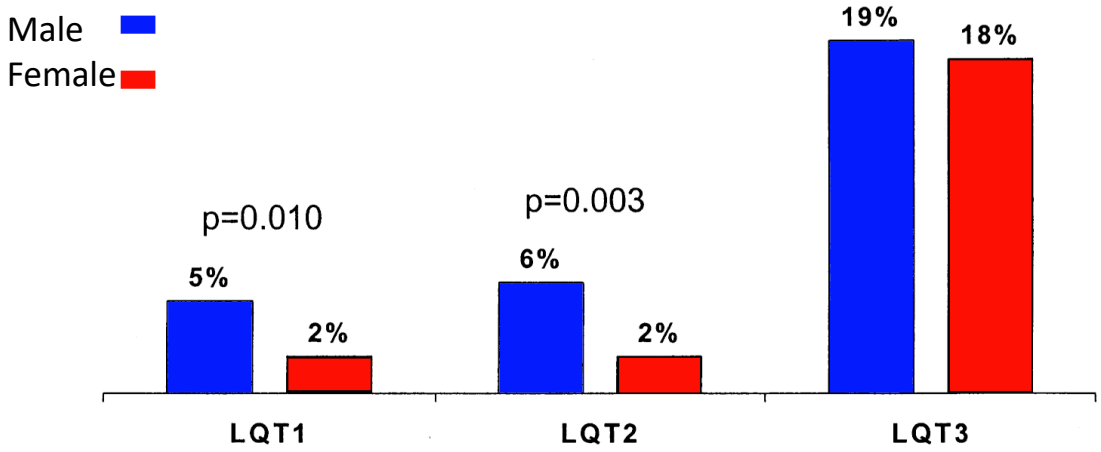
Modulating Effects of Age and Gender on the Clinical Course of Long QT Syndrome by Genotype



The **lethality of cardiac events** analyzed by sex in long QT syndrome (LQTS) **family members** with known genotype



Zareba W, et al. J Am Coll Cardiol 2003;42:103–9

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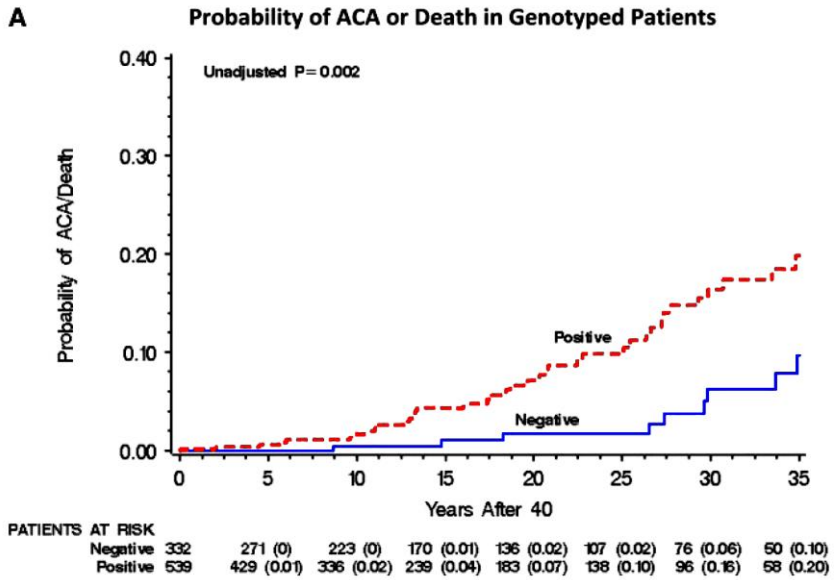
Long-QT Syndrome After Age 40

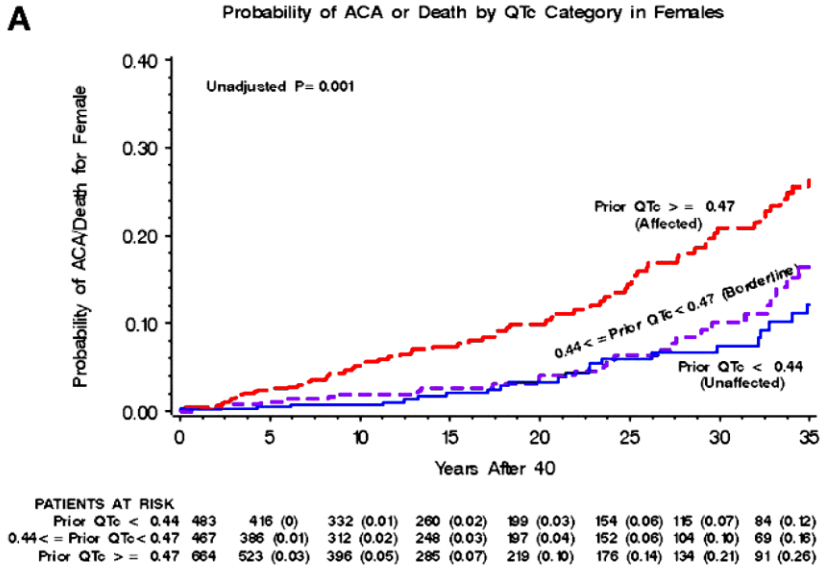
2759 subjects from the International LQTS Registry

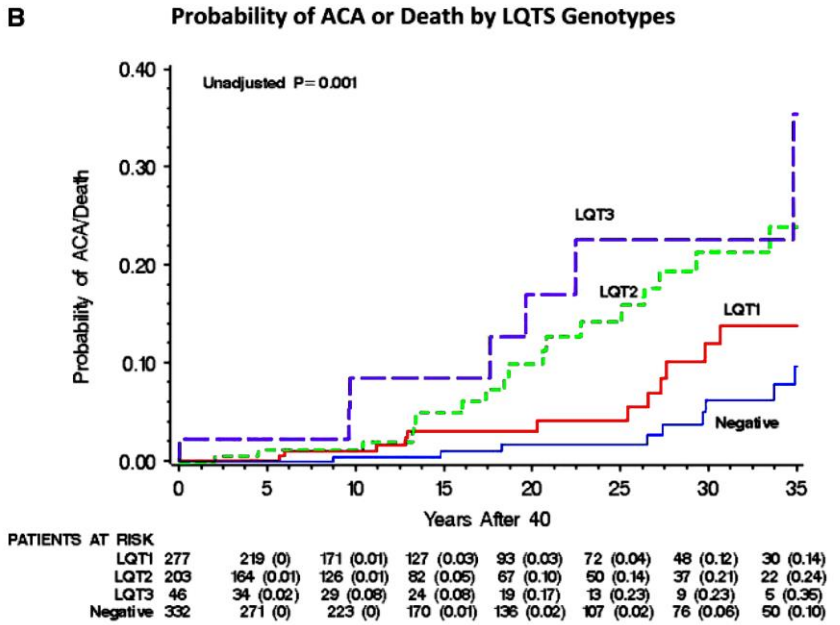
Multivariable Analysis: Predictors of ACA or Death After Age 40 Years: Risk in Total Population by ECG Presence of LQTS

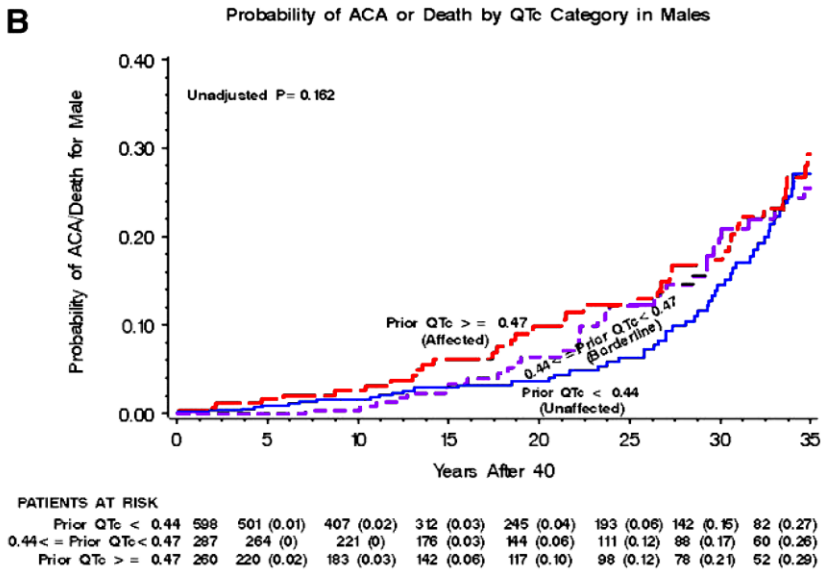
	41–60 y (n = 2759)		61–75 y (n = 1132)	
group	HR	P	HR	P
A vs U	2.65	<0.001	1.23	0.31
A vs B	1.36	0.28	1.08	0.71

A = QTc≥470ms; B = QTc 440-469ms;
U = QTc<440ms; HR = hazard ratio









Goldenberg I, et al. Circulation. 2008;117:2192-2201

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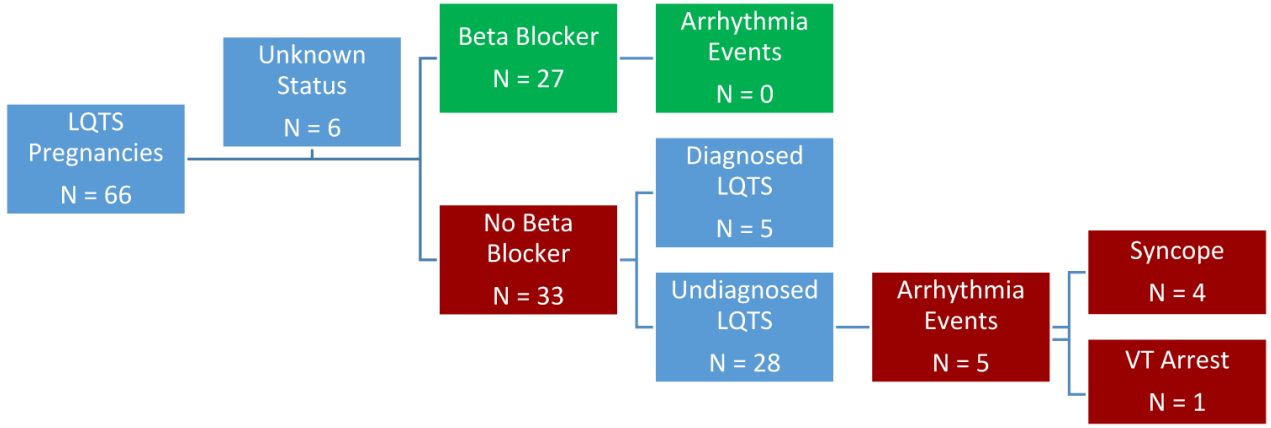
Contemporary maternal and fetal outcomes in the treatment of LQTS during pregnancy: Is nadolol bad for the fetus?

Flowchart showing outcomes of patients with long QT syndrome (LQTS) during pregnancy



ß-Blocker therapy in fetuses with and without IUGR

Variable	IUGR (n = 12)	No IUGR (n = 31)	P
ß-Blocker	8	12	0.08
Nadolol	4	8	
Propranolol	3	1	
Metoprolol	1	2	
Atenolol	0	3	
No ß-blocker	3	17	
Unknown	1	2	

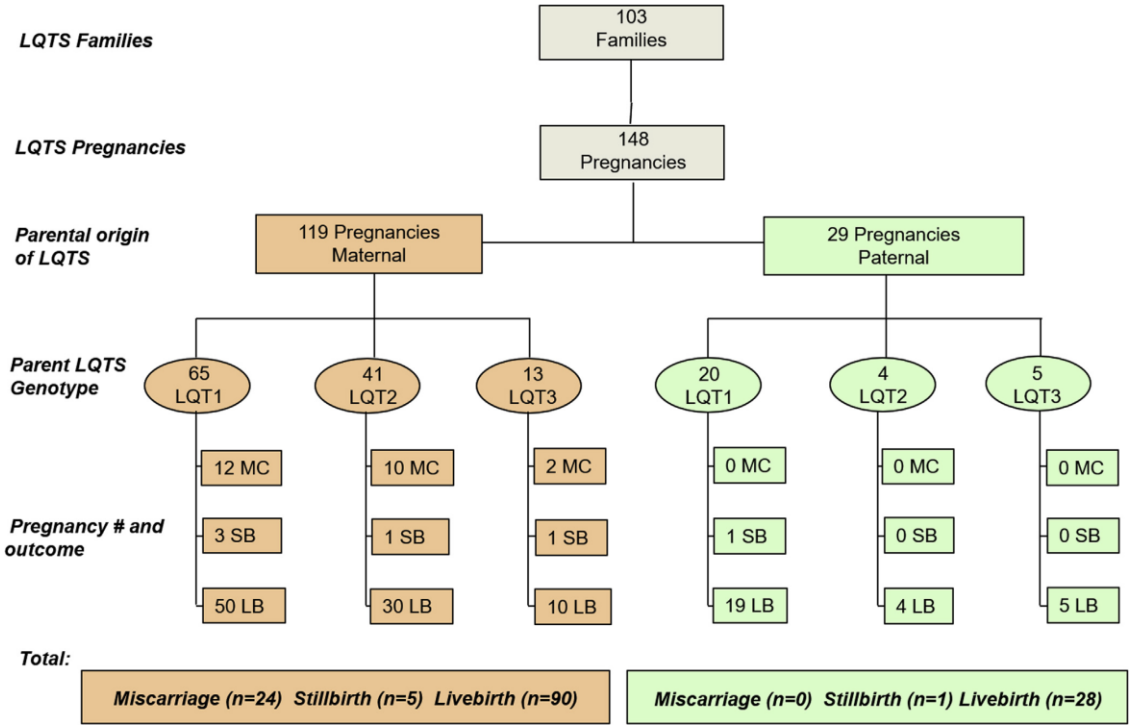
IUGR = intrauterine growth restriction.

Conclusion

1. **Arrhythmic events** were only seen in the **postpartum period** in those **not treated with ß-blockers**.
2. ß-Blocker therapy, specifically **nadolol**, was **not associated** with a higher incidence of **intrauterine growth restriction**.
3. Neonatal bradycardia was rare, and hypoglycemia was not observed.

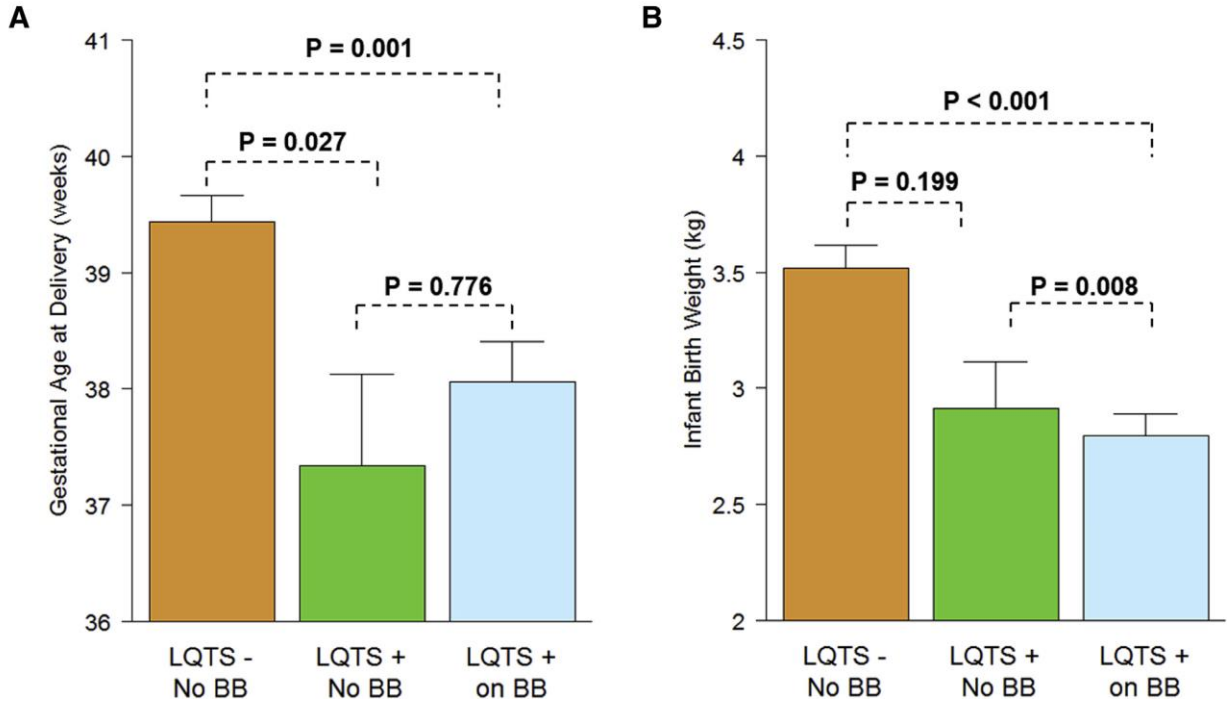
Mothers with long QT syndrome are at increased risk for fetal death: findings from a multicenter international study

Flow chart of the study population



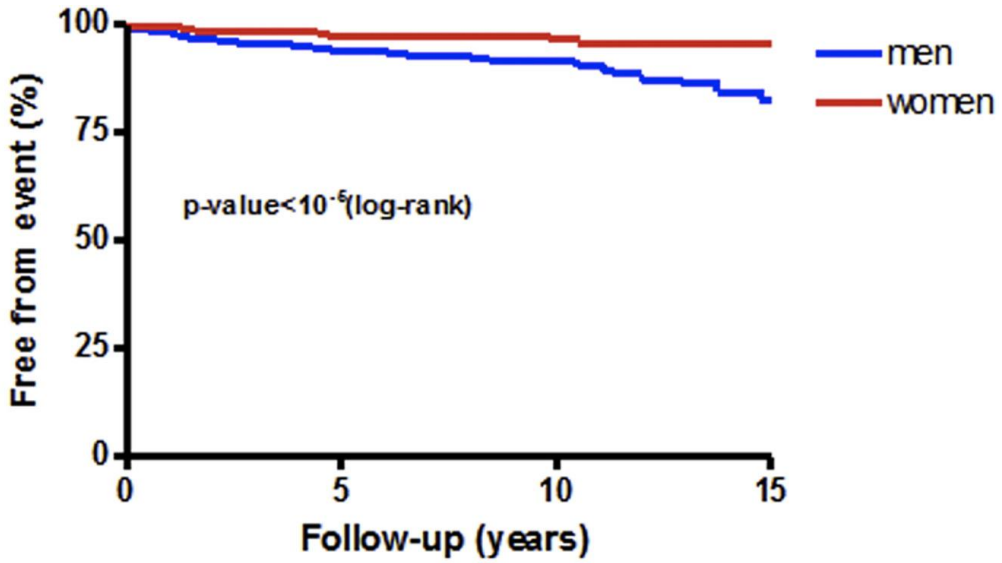
Stillbirths (>20 w GA); LQTS : Control = 4% : 0.5% (X 8)
Miscarriages (≤20 w GA); LQTS : Control = 16% : 8% (X 2)
Fetal death; maternal : paternal LQTS =24.4% : 3.4% (P =.036)

Effect of ß-blocker therapy during pregnancy on fetal outcomes



Cuneo BF. et al. Am J Obstet Gynecol. 2020;222(3):263.e1-263.e11.

Univariate and multivariate analyses of the risk factors of sudden cardiac death in women with BrS



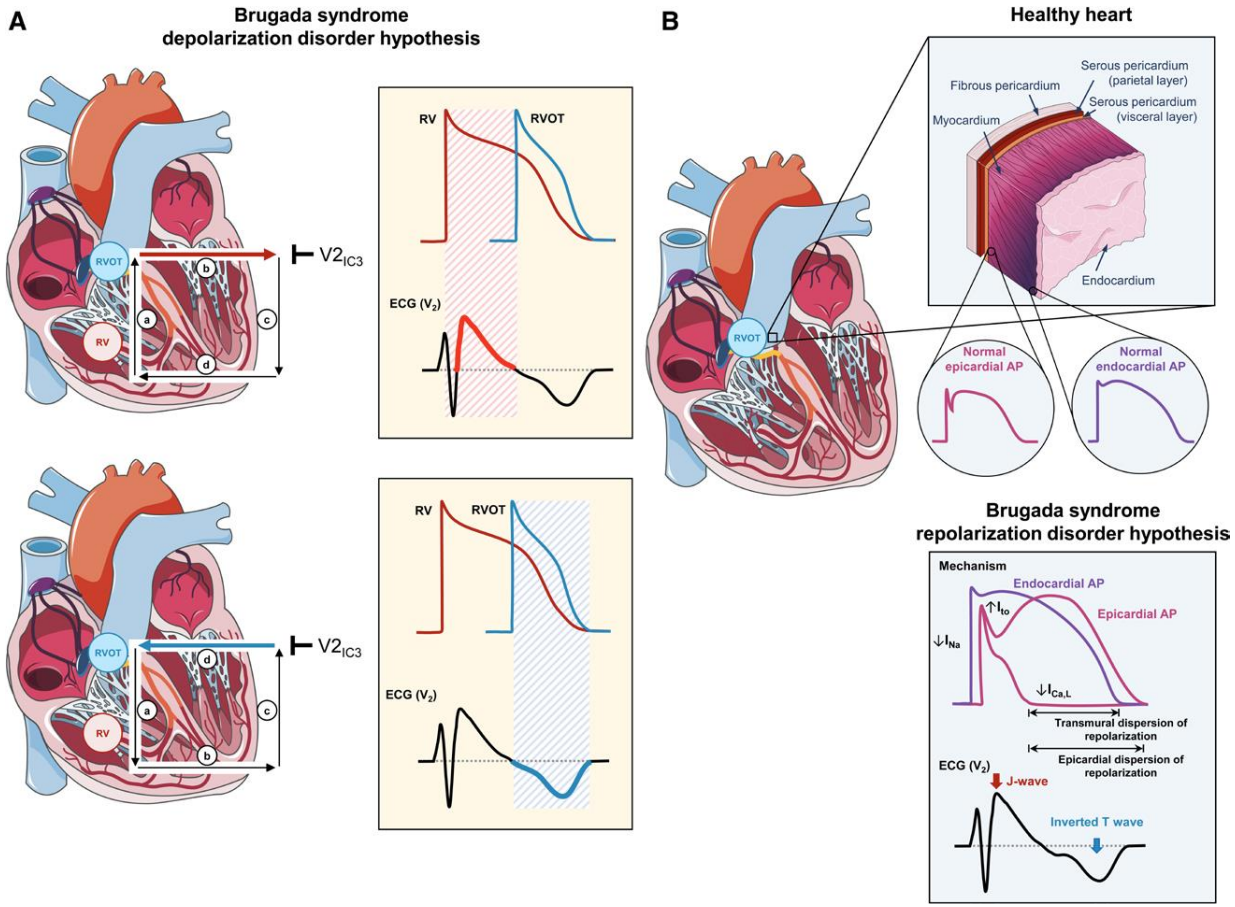
	Univariate analysis			Final multivariate analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age (increase of 10 y)	1	0.7–1.4	0.92			
Index case	4.6	1.0–21.2	0.05	10.2	1.7–61.4	0.01
SCD or VA	47.5	12.7–177.6	<.0001	69.4	15–321.5	<.0001
Syncope	5.3	1.2–23.9	0.03	6.8	1.3–34.4	0.02
Family history of BrS	1.7	0.4–7.1	0.16			
Family history of SCD	2	0.6–6.2	0.25			
Sinus node dysfunction	18.1	4.0–82.9	0.0002			
ICD	37.1	4.8–288.1	0.0006			
Positive EPS†	1.3	0.2–7.2	0.76			
Positive *SCN5A* mutation‡	1.2	0.4–4.0	0.77			
Spontaneous type 1	2.5	0.8–7.9	0.12			
Type 1 peripheral leads	11.1	2.4–50.9	0.0002			
PR >200 ms in D2	0.9	0.2–4.3	0.93			
QRS >120 ms in D2	5.8	1.8–19.4	0.004	4.7	1.2–19.5	0.03
TPEmax >100 ms	1.7	0.5–5.2	0.37			
QTc >460 ms	1.3	0.2–10.1	0.8			
Fragmented QRS	8.8	1.1–68.9	0.04	20.2	1.8–228.9	0.02
aVR sign	4.9	1.6–15.7	0.007			

ICD = implantable cardioverter–defibrillator; SCD = sudden cardiac death; TPE = Tpeak–Tend interval; aVR sign = R ≥ 0.3 mV or R/q ≥ 0.75 in the aVR lead. † Of patients who underwent the test. ‡ Of patients tested for *SCN5A* mutation.

Berthome P, et al. Heart Rhythm 2019;16:260–267

Sex-Related Differences in Cardiac Channelopathies

Schematic representation of proposed mechanisms underlying BrS



Sex differences in BrS in clinical phenotypes

- clinical expression (F : M = 1 : 8 – 10 times)
- time of diagnosis (F : M = 49 : 43 years)
- first arrhythmic event (F : M = 50 : 43 years)
- spontaneous type 1 (F : M = 22 - 41 : 36 - 69 %)
- VA inducibility (F : M = 27 - 36 : 42 - 66 %)
- pediatric age group: spontaneous BrS ECG, earlier onset of arrhythmic events (girls > boys)

***SCN5A* pathogenic variant in female patients may become a higher arrhythmic risk**

- *SCN5A* pathogenic variants in asymptomatic patients; F : M (27% : 21%)
- Arrhythmic events; F : M (48% : 28%)

testosterone: $I_{to}(\uparrow)$, $I_{Ca,L}(\downarrow)$

estrogen: $I_{to}(\downarrow)$, $I_{Ca,L}(\uparrow)$

Asatryan B, et al. Circulation. 2021;143:739–752.

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The Clinical Significance of Pregnancy in Brugada Syndrome

Baseline Characteristics of the Population Enrolled in the Study

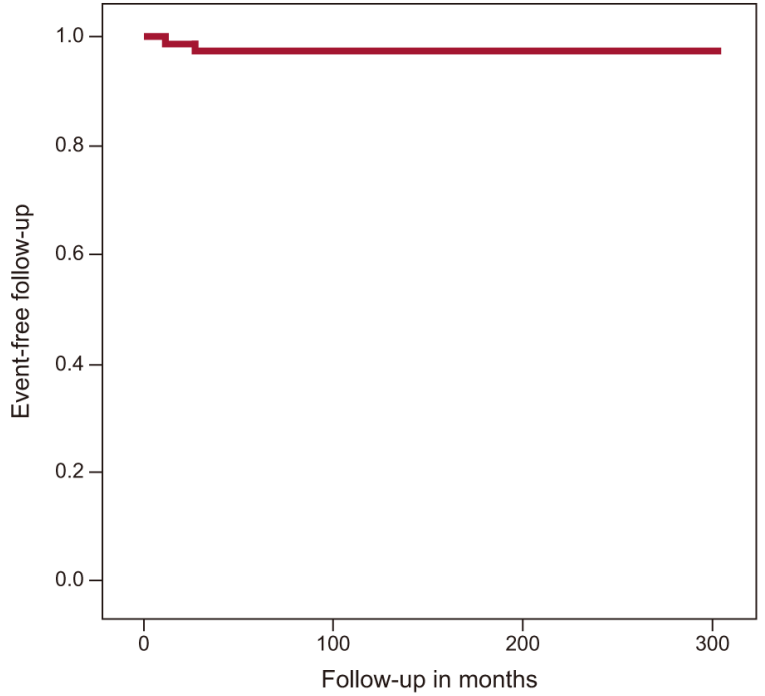
Patients, n	104
Age, years	43.3 ± 12.9
Proband	29 (27.8)
Family history of SCD	66 (63.4)
SCN5A positive	14 (13.4)
Asymptomatic	59 (56.7)
Previous syncope	24 (23.1)
Aborted SCD	4
Palpitations-presyncope	17 (16.3)
Age first symptom	42.8 ± 12.8
EPS study	86 (82.6)
VT/VF induction in the EPS	7 (6.7)
ICD implantation	27 (26)
Baseline type I ECG	7 (6.7)
PR interval, ms	163.4 ± 27.2
QRS interval, ms	92.1 ± 17.8
cQT V1, ms	393.7 ± 37.5
cQT lead II, ms	404.9 ± 27.4

Description of Deliveries and Events During Pregnancy in the Study Sample

Number of partus	212
Spontaneous abortus	15
Age first partus, years	24.9 ± 3.9
Cesarean	13
Vaginal partus	175
Events	13
Syncope	11
Tachycardia	2
SCD	0
SID	1

ECG, electrocardiogram; EPS, electrophysiological study; ICD, implantable cardiac defibrillator; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia; SCD, sudden cardiac death; SID, sudden infant death

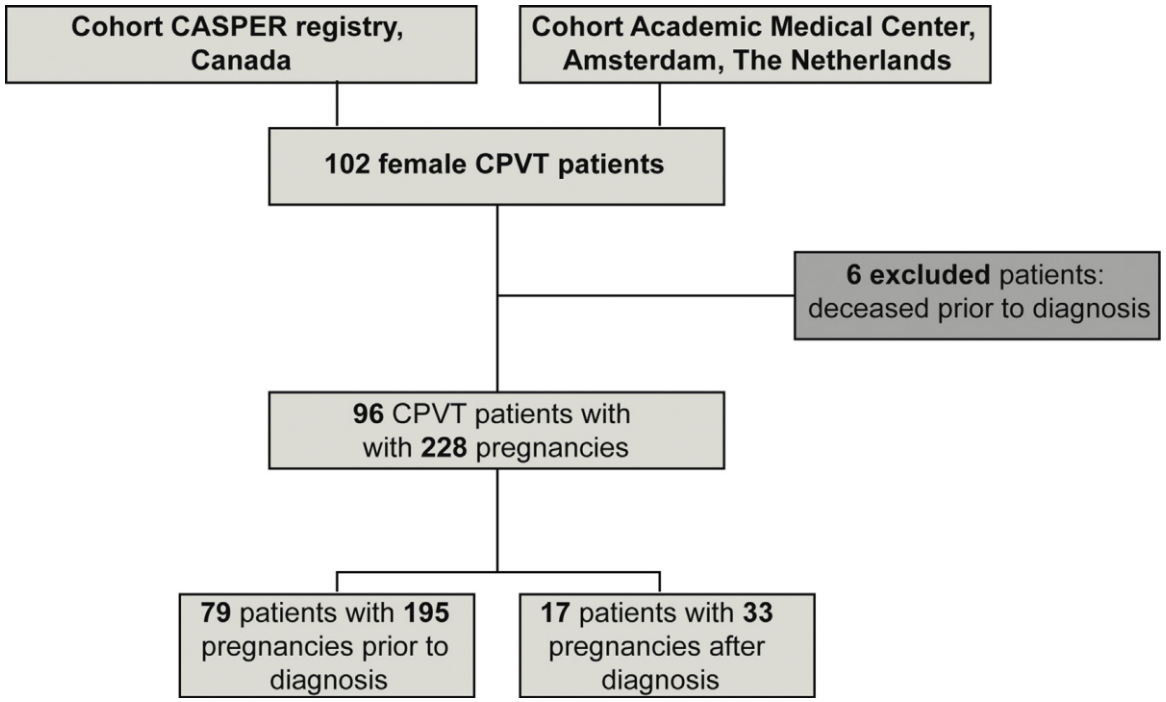
Kaplan-Meier analysis of cardiac events in the follow-up



Conclusion: Serious events were not more frequent during pregnancy and the peripartum period in women with Brugada syndrome. The occurrence of syncope during pregnancy was not associated with a worst outcome in the peri- and postpartum periods or during follow-up.

Rodriguez-Manero M, et al. Rev Esp Cardiol. 2014;67(3):176–180

Pregnancy in Catecholaminergic Polymorphic Ventricular Tachycardia



Event Rates During Pregnant, Postpartum, and Nonpregnant Periods

Time Period	Duration (patient-years)	Event Rate (per 100-patient-years)	Rate Ratio (95% CI)*	p Value
Pregnancy	177.4	1.71	1.17 (0.24–4.71)	0.802
Postpartum	105.2	2.85	1.96 (0.40–7.85)	0.362
Combined pregnancy and postpartum	280.6	2.14	1.47 (0.45–4.81)	0.518
Nonpregnant†	411.4	1.46	1	N/A (reference)

*Rate ratio compared with nonpregnant period event rate. †Nonpregnant period defined as total follow-up minus pregnancy and postpartum periods. Combined pregnancy and postpartum period includes pregnancy (assuming 40-week gestation) and postpartum period (assuming 24 weeks). CI = confidence interval.

Conclusion The combined pregnancy and postpartum arrhythmic risk in CPVT patients was not elevated compared with the nonpregnant period.

Cheung CC. et al. J Am Coll Cardiol EP 2019;5:387–94

Conclusion

- Early diagnosis, preventive treatment, and management are essential in patients with inherited arrhythmias that may cause sudden cardiac death in the young.
- Some of the inherited arrhythmias have sex differences regarding the age of the onset and prognosis. This hormonal change is most distinct in the adolescent period, which may result in life-threatening events.
- Women with inherited arrhythmias may need to continue drug treatment and device management during the pregnancy, delivery, and post-partum period, and also we have to consider the adverse drug effects on the fetus, miscarriages, stillbirths, and sudden infant death. Fortunately, nonselective ß blockers have little or minor adverse effects on pregnant women and the fetus.