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Implications for Clinical Practice

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Author(s): Babken Asatryan, Inselspital, Bern University Hospital

Lauren Yee, University of British Columbia

Yael Ben-Haim, St. Georges University of London

Stephan Dobner, Inselspital Bern, Department of Cardiology

Helge Servatius, University Hospital Bern

Laurent Roten, Department of Cardiology, Inselspital, Bern

University Hospital, and University of Bern, Switzerland

Hildegard Tanner, University Hospital Bern

Lia Crotti, University Milano Bicocca

Jonathan Skinner, Starship Children's Hospital

Carol Ann Remme, Academic Medical Center, Amsterdam  
Philippe Chevalier, Louis Pradel Cardiology Hospital, Bron, Hospices  
Civils de Lyon, Lyon, France

Argelia Medeiros-Domingo, Swiss DNAlysis

Elijah Behr, St George's University of London

Tobias Reichlin, Inselspital, Bern University Hospital

Katja Odening, Department of Cardiology, Inselspital, Bern  
University Hospital, and University of Bern, Switzerland

Andrew Krahn, University of British Columbia

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# Sex-Related Differences in Cardiac Channelopathies: Implications for Clinical Practice

**Short title:** Sex Differences in Cardiac Channelopathies

Babken Asatryan, MD, PhD<sup>1</sup>; Lauren Yee, BSc<sup>2</sup>; Yael Ben-Haim, MD<sup>3,4</sup>; Stephan Dobner, MD, PhD<sup>1</sup>;  
Helge Servatius, MD<sup>1</sup>; Laurent Roten, MD<sup>1</sup>; Hildegard Tanner, MD<sup>1</sup>; Lia Crotti, MD, PhD<sup>4,5,6,7</sup>;  
Jonathan R. Skinner, MBChB, DCH, MD<sup>8,9,10</sup>; Carol Ann Remme, MD, PhD<sup>11</sup>; Philippe Chevalier, MD, PhD<sup>4,12,13,14</sup>  
Argelia Medeiros-Domingo, MD, PhD<sup>15</sup>; Elijah R. Behr, MBBS, MD<sup>3,4,16</sup>; Tobias Reichlin, MD<sup>1</sup>;  
Katja E. Odening, MD<sup>1,\*</sup>; Andrew D. Krahn, MD<sup>2,\*</sup>

1. Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
2. Heart Rhythm Services, Division of Cardiology, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada
3. Institute of Molecular and Clinical Sciences, St. George's University of London, London, United Kingdom
4. European Reference Network for Rare and Low Prevalence Complex Diseases of the Heart: ERN GUARD-Heart
5. Istituto Auxologico Italiano, IRCCS, Center for Cardiac Arrhythmias of Genetic Origin and Laboratory of Cardiovascular Genetics, Milan, Italy
6. Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy
7. Istituto Auxologico Italiano, IRCCS, Department of Cardiovascular, Neural and Metabolic Sciences, San Luca Hospital, Milan, Italy
8. The Cardiac Inherited Disease Group, Auckland, New Zealand
9. Greenlane Paediatric and Congenital Cardiac Services, Starship Children's Hospital, Auckland, New Zealand
10. Department of Paediatrics, Child and Youth Health, University of Auckland, New Zealand
11. Heart Center, Department of Clinical and Experimental Cardiology, Amsterdam UMC, location AMC, University of Amsterdam, Amsterdam, The Netherlands
12. Department of Rhythmology, Hospices Civils de Lyon, Louis Pradel Cardiovascular Hospital, Lyon, France
13. Lyon Reference Center for Inherited Arrhythmias, Louis Pradel Cardiovascular Hospital, Bron, France
14. Université de Lyon, Lyon, France
15. Swiss DNALysis, Dübendorf, Switzerland
16. Cardiology Clinical Academic Group, St. George's University Hospitals NHS Foundation Trust, London, United Kingdom

\* Drs. Odening and Krahn contributed equally.

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## **Correspondence:**

Babken Asatryan, MD, PhD  
Department of Cardiology  
Inselspital, Bern University Hospital, University of Bern  
Freiburgstrasse 18, 3010 Bern, Switzerland  
Tel.: +41 31 632 84 37; Fax: +41 31 632 42 11  
Email: [babken.asatryan@insel.ch](mailto:babken.asatryan@insel.ch)

## **Abstract**

Sex-related differences in prevalence, clinical presentation and outcome of cardiac channelopathies are increasingly recognized, despite their autosomal transmission and hence equal genetic predisposition among sexes. In congenital long QT syndrome, adult women carry a greater risk for torsades de pointes and sudden cardiac death (SCD), than men. In contrast, Brugada syndrome is predominantly observed in adult men, with a considerably higher risk of arrhythmic SCD in adult men than in women. In both conditions, the risk for arrhythmias varies with age. Sex-associated differences appear less evident in other cardiac channelopathies, likely a reflection of their rare(r) occurrence and our limited knowledge. In several cardiac channelopathies, sex-specific predictors of outcome have been identified. Together with genetic and environmental factors, sex hormones contribute to the sex-related disparities in cardiac channelopathies through modulation of the expression and function of cardiac ion channels. Despite these insights, there are still essential knowledge gaps in the mechanistic understanding of these differences, warranting further investigation. Precise application of the available knowledge may improve the individualized care of patients with cardiac channelopathies. Promoting the reporting of sex-related phenotype and outcome parameters in clinical and experimental studies and advancing research on cardiac channelopathy animal models should translate into improved patient outcomes. This review provides a critical digest of the current evidence on sex-related differences in cardiac channelopathies, with an emphasis on their clinical implications and remaining gaps requiring further research.

**Keywords:** cardiac arrhythmia; genetics; sex; gender; Long QT syndrome; Brugada syndrome; sudden cardiac death

## **Non-standard Abbreviations and Acronyms**

APD = action potential duration

BrS = Brugada syndrome

CPVT = catecholaminergic polymorphic ventricular tachycardia

EAD = early afterdepolarization

ECG = electrocardiogram

HR = hazard ratio

ICD = implantable cardioverter defibrillator

LQTS = congenital Long QT syndrome

QTc = heart-rate corrected QT interval

RVOT = right ventricular outflow tract

SADS = sudden arrhythmic death syndrome

SCD = sudden cardiac deaths

SQTS = short-QT syndrome

TdP = torsades de pointes

VF = ventricular fibrillation

VT = ventricular tachycardia

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## 1. Introduction

Cardiac channelopathies are heritable disorders caused by pathogenic variants in genes encoding cardiac ion channel subunits and ancillary proteins that maintain the electromechanical function of human cardiomyocytes.<sup>1</sup> Collectively, cardiac channelopathies are estimated to underlie up to 10% of all sudden cardiac deaths (SCD),<sup>2</sup> most of which occur in individuals younger than 40 years of age.<sup>3,4</sup> Cardiac channelopathies are typically inherited in an autosomal dominant manner, meaning that first-degree family members have a 50% chance of inheriting the variant that predisposes to disease.<sup>1</sup> Most cardiac channelopathies show incomplete penetrance and variable expressivity whereby family members, who carry the same variant sometimes have a wide range of different phenotypes.<sup>5,6</sup>

A wide array of genetic, post-translational and environmental factors that influence the cardiac channelopathy phenotype is being recognized ([Figure 1](#)).<sup>6</sup> Emerging evidence suggests that biological sex, partly due to genetic and environmental factors and partly through the multifaceted effects of sex hormones on cardiac ion channels, is important in determining clinical course in cardiac channelopathies.<sup>7-10</sup> Furthermore, men and women with certain cardiac channelopathies show differences in age-related penetrance, disease expression and risk for SCD.<sup>11</sup> Nonetheless, there is limited awareness of sex-related differences in clinical manifestations of cardiac channelopathies and risks in different reproductive phases in life. Findings from large cohort studies are often extrapolated to both sexes without considering relevant sex-related variances.

In this review, we summarize the compelling evidence for sex-related differences and their underlying mechanisms in cardiac channelopathies, their clinical implications for patient management, and how future research relevant to the elucidation of sex as a modifier of phenotype can improve the precision of care of cardiac channelopathy patients.

## 2. Sex differences in normal cardiac electrophysiology parameters

Significant sex-related differences in electrocardiographic features have been recognized for decades. Men have longer PR intervals, P-wave and QRS-durations, than women, whereas resting heart rate is higher and heart-rate corrected QT intervals (QTc) are longer in adult women.<sup>12</sup> While QTc is similar in boys and girls at birth and during childhood, sex-related differences become evident with the onset of puberty due to QT shortening in males and QT prolongation in females, and diminish after menopause, indicating an impact of sex hormones, particularly testosterone, on cardiac repolarization.<sup>12-14</sup> Additionally, at puberty, boys develop a typical pattern of ventricular repolarization, characterized by a higher amplitude of the J-point, a shorter and steeper ST segment course, a steeper ascent, and a higher amplitude of the T wave.<sup>15</sup> The QT interval is also affected by the menstrual cycle, with shorter durations observed in the luteal than in the follicular phase, attributed mainly to the increased progesterone levels during the luteal phase.<sup>16</sup> In addition, the QT/RR slope is steeper in women than in men, such that sex differences in QTc are more pronounced at slow heart rates.<sup>17</sup>

Sex-specific variations in normal cardiac electrophysiology and susceptibility to arrhythmias have mainly been ascribed to genetic factors and hormonal influences. Differences in autonomic tone, hemodynamics, non-steroid hormone levels and homeostatic response to defective ion channels (e.g. changes in expression of other ion channels) may also contribute to sex-related disparities, but these mechanisms are not yet fully understood.

### 3. Long QT Syndrome

Congenital Long QT Syndrome (LQTS) is a primary disorder of cardiac repolarization characterized by a prolonged QT interval on the surface electrocardiogram (ECG) and predisposition to arrhythmic syncope, torsades de pointes (TdP) and SCD at a young age.<sup>18</sup> While seventeen genes have been implicated in LQTS, in a recent evidence-based assessment, only three genes – *KCNQ1*, *KCNH2* and *SCN5A* – were found to have definitive evidence for causing typical LQTS.<sup>19</sup> Variants in these three genes collectively explain about 90% of all genotype-positive cases.<sup>20</sup> *KCNQ1* (LQT1) and *KCNH2* (LQT2) encode the  $\alpha$ -subunits of voltage-gated repolarizing  $K^+$  channels conducting  $I_{Ks}$  and  $I_{Kr}$  respectively, whereas *SCN5A* (LQT3) encodes the  $\alpha$ -subunit,  $Na_v1.5$ , of the cardiac  $Na^+$  channel, conducting  $I_{Na}$ , and in case of variants, pathological late  $I_{Na,L}$ .<sup>18</sup>

#### *Sex-related differences in clinical phenotype*

Significant sex-related differences in the QT-interval, as well as implications for sex-based risk assessment and management, are well recognized in LQTS. Because of the longer QT intervals in healthy women, sex-specific cut-offs for defining a prolonged QT interval were determined – 470ms in males and 480ms in females (Figure 2).<sup>21</sup> Among LQTS variant carriers, the clinical penetrance of disease is higher in females than in males.<sup>7</sup> In the largest multicenter registry reported so far, females comprised 56% of all LQTS patients (Figure 3).<sup>22, 23</sup> As in the general population, women with LQTS (particularly LQT1 and LQT2) have longer QTc intervals than their male counterparts.<sup>29</sup> Females are more prone to QT prolongation at slower heart rates; therefore, evaluation of QTc at rest, particularly at night, is important for risk stratification.<sup>29</sup> Furthermore, adult females with LQTS are generally at increased risk of TdP compared to males and pre-pubescent females.<sup>30</sup>

In general, male LQTS patients have a greater risk of fatal presentation of the disease, while females typically experience recurrent, non-fatal events, such as syncopal episodes, likely related to self-terminating TdPs.<sup>7</sup> In childhood and prior to puberty, males with LQT1 have an increased risk for arrhythmias compared to females but the risk of arrhythmias is similar in males and females with LQT2 or LQT3;<sup>11</sup> however, after puberty, the risk of experiencing arrhythmias in LQT1 patients reverses, with females being at higher risk.<sup>7</sup> Post-pubertal females with LQT2 have a higher risk for ventricular arrhythmias compared to men,<sup>11</sup> and the risk stays elevated after menopause,<sup>31</sup> implying that there is a need for life-long therapy in these patients.

Studies have found that men with LQT1 and LQT2 present earlier in life with a cardiac phenotype than their female counterparts.<sup>32</sup> LQT2 females and LQT3 males are both at elevated risk of experiencing an arrhythmic event before age 40 than their LQT2 male and LQT3 female counterparts, respectively.<sup>32</sup> In LQT3, females are at higher risk for SCD, particularly in the 30-40 year age group.<sup>33</sup>

Female sex has also been shown to increase the risk of TdP associated with cardiovascular<sup>34</sup> and non-cardiovascular drugs.<sup>35</sup> Furthermore, a study investigating a large cohort of patients with acquired atrioventricular block found relevant sex differences in the association of QT interval duration with the risk of TdP at bradycardia.<sup>36</sup> While longer QTc intervals were associated with a higher risk of TdP in both sexes, females were susceptible to TdP at shorter QTc durations that were not necessarily arrhythmogenic for males, indicating that female sex is an independent predictor of TdP.<sup>36</sup>

### ***Hormonal influences underlying sex-related differences***

Although the exact mechanisms for all sex-related disparities remain uncertain, sex hormones are known to modulate the phenotype in LQTS ([Figure 4](#)).<sup>13</sup> In animal models, estrogen increased the duration of the QT interval through mechanisms similar to its physiological effect on ionic currents ([Table 1](#)), whereas endogenous progesterone and testosterone shortened the QT interval,<sup>13</sup> thus having a protective effect in LQT1 and LQT2 patients. The lack of sex-specific differences with QTc interval durations and SCD risk between male and female patients with LQT3, at least in part, can be explained by the fact that estrogen, the main hormone driving the increased risk of TdP in LQTS females, modulates principally  $I_{Ks}$  and  $I_{Kr}$  and to a much lesser degree  $I_{Na}$ , the current affected in LQT3.<sup>13</sup>

Sex-related differences in LQTS have been studied in several animal models. In LQT1 rabbits, no sex differences were present in QT duration, whereas in LQT2, sex differences similar to those seen in humans were present.<sup>37</sup> Female LQT2 rabbits showed a steeper QT/RR relationship, resulting in longer QT-duration at slower heart rates.<sup>38</sup> As in LQT2 patients, in transgenic LQT2 rabbits ventricular arrhythmia and SCD often occurred in the postpartum period.<sup>37, 39</sup> In these models, estradiol increased the incidence of lethal TdP arrhythmias by changing the pattern of APD dispersion and increasing early afterdepolarization (EAD) formation during sympathetic stimulation. Progesterone had an antiarrhythmic effect that was based on shortening of cardiac refractoriness, reduced formation of EAD, and stabilization of  $Ca^{2+}$ -related effects (decreased  $I_{Ca,L}$  density, increased SERCA expression).<sup>39</sup> Studies investigating the effects of postpartum-related hormones oxytocin and prolactin on cardiac electrophysiology in LQT2 rabbits demonstrated a pro-arrhythmic QT/APD-prolongation of both hormones due to  $I_{Ks}$ -blocking properties.<sup>40</sup>



## **Management**

While therapy with  $\beta$ -blockers should be offered in both boys and girls upon diagnosis, it should be noted that asymptomatic preadolescent boys with a QTc duration  $>500$  ms exhibit a  $>12$ -fold increase in the risk of life-threatening cardiac events compared with the respective girls; this indicates the importance of urgent initiation of therapy in these patients.<sup>41</sup> In selected cases, asymptomatic adult males with LQTS, particularly those with older age at diagnosis and QTc  $<470$  ms, may benefit from  $\beta$ -blocker dose reduction (or even discontinuation),<sup>42</sup> considering the lower risk observed at this age<sup>7</sup> and the well-recognized dose-dependent side effects of beta-blockers. Females, however, might have increased risk after puberty and need attentive evaluation for more aggressive therapy, given the increased QTc duration mediated by the influence of sex hormones.

All LQTS patients, but particularly those with LQT2, should consider  $K^+$  supplementation. In those with significant and frequent decrease in  $K^+$  levels, therapy with  $K^+$  sparing diuretics like aldosterone can be a useful add-on therapy.  $\beta$ -Blockers (particularly nadolol) are the mainstay of therapy in LQTS.<sup>1</sup> Therapy with  $\beta$ -blockers is generally effective, particularly in those with LQT1, where they are virtually curative, but also in LQT2 with a 70-80% efficacy.<sup>11</sup> Response to  $\beta$ -blockade varies by sex and genotype, as adult LQT1 males have the greatest QTc shortening upon treatment with  $\beta$ -adrenoceptor blockade.<sup>43</sup>

In LQT3,  $\beta$ -blocker therapy has been reported to result in an 83% reduction in cardiac events in females but not in males (who, however, had many fewer events).<sup>33</sup> Individuals with poor adherence to  $\beta$ -blockers may benefit from a left cardiac sympathetic denervation. Alternatively, mexiletine can be used in LQT3 patients, particularly if they are symptomatic or exhibit a QTc  $>500$  ms despite  $\beta$ -blockade.<sup>44, 45</sup> Limited evidence suggests that flecainide therapy is safe and effective in LQT3; it can be used as an alternative therapy unless patients exhibit flecainide-induced Brugada pattern, which is relatively common in males.<sup>46</sup> Implantable cardioverter defibrillators (ICD) are recommended for survivors of cardiac arrest as well as for patients at high-risk for SCD.<sup>1</sup>

In LQTS females, until more data becomes available, the possible QTc-prolonging effect of synthetic progesterone should be considered when deciding upon the mode of contraception.<sup>47</sup> Men with LQTS should be evaluated for low serum testosterone levels, androgen deprivation therapy exposure, and endocrine disorders associated with hypogonadism, since these factors have been associated with higher risk for drug-induced TdP,<sup>48, 49</sup> and might represent modifiable risk factors in men with congenital LQTS. A recent small placebo-controlled study showed that transdermal testosterone attenuates the QT-prolonging effects of ibutilide in older men, suggesting that androgens might be useful to prevent or treat TdP in men with drug-induced LQTS.<sup>50</sup> Whether these results have relevance to congenital LQTS remains to be investigated.

## ***Pregnancy***

Females are at a decreased risk of cardiac events during pregnancy, particularly those with LQT1.<sup>51</sup> The risk for arrhythmic events is however elevated in the post-partum period, especially in patients with LQT2.<sup>51</sup> Following the post-partum period, the risk of LQTS-related arrhythmias decreases, returning to the pre-pregnancy baseline.<sup>51</sup>  $\beta$ -Blockade mitigates the risk of arrhythmias during pregnancy and the high-risk post-partum period.<sup>51</sup> Whereas non-selective  $\beta$ -blockers are recommended for the post-partum period, metoprolol has the most fetal safety data.<sup>52</sup> Broader safety data of propranolol and the limited evidence for its safety in LQTS pregnancies<sup>53</sup> suggest that it might be the best option given its higher efficacy in LQTS. This disparity in the safety of metoprolol and efficacy of non-selective  $\beta$ -blockers (nadolol and propranolol) is not resolved, with good experience by the authors with non-selective  $\beta$ -blockers.<sup>54</sup> Generally,  $\beta$ -blockers are well tolerated during pregnancy and the post-partum period with slightly lower fetal birth weights.  $\beta$ -blockers are secreted in breast milk, so fetal hypoglycemia is an uncommon consequence of maternal  $\beta$ -blocker administration.

Mothers with LQTS have an 8-fold increased risk for stillbirth (fetal death at >20 weeks gestation; 4% vs 0.5%), and a 2-fold higher risk for miscarriages (fetal death at  $\leq$ 20 weeks gestation; 16% vs. 8%) than the general population.<sup>55</sup>

## **4. Brugada Syndrome**

Brugada syndrome (BrS) is a genetic arrhythmia syndrome characterized by coved-type ST-segment elevation followed by a negative T-wave in the right precordial leads (V<sub>1</sub>-V<sub>3</sub>), either spontaneously or provoked by a sodium channel blocker, and increased susceptibility to SCD due to polymorphic ventricular tachycardia (VT) or VF.<sup>56</sup> Although 21 genes have been previously reported in association with BrS,<sup>20</sup> a recent evidence-based reappraisal of gene-disease validity disputed the causality of 20 genes, leaving *SCN5A* as the only gene with definite causality in BrS.<sup>57</sup> Variants in *SCN5A* underlie 20% of all BrS cases.<sup>58</sup>

### ***Sex-related differences in clinical phenotype***

Although both sexes are theoretically at similar risk to carry variants that predispose to BrS, clinical disease expression is 8-10 times higher in males ([Figure 3](#)).<sup>59</sup> Because of the overwhelming predominance of males among BrS patients, there are few data on sex differences in disease phenotype. It is, however, recognized that women with BrS are more frequently asymptomatic at the time of diagnosis, and 6-7 years older than men both at the time of diagnosis (49 vs. 43 years) and with first arrhythmic event (50 vs. 43 years).<sup>25, 26</sup> Female BrS patients less frequently have a spontaneous type 1 Brugada ECG pattern (22-41% vs 36-69%) or ventricular arrhythmia inducibility at electrophysiology study (27-36% vs 42-66%).<sup>26, 60</sup> Moreover, females are 3-4 times less likely to experience arrhythmic events, namely syncope, aborted cardiac arrest and documented VF, than their male counterparts.<sup>26, 61</sup> An exception to the male-predominant arrhythmic risk is the pediatric age

group, in which a spontaneous BrS ECG was shown to be associated with earlier onset of arrhythmic events – in particular, associated with fever – in females compared to males.<sup>60</sup> Therefore, while the age of first arrhythmic event is normally distributed in men, the female distribution is bi-modal.<sup>25</sup> It remains unclear whether sex distinction also extends to risk/prevalence of atrial arrhythmias, particularly atrial fibrillation. Studies on atrial fibrillation incidence in BrS included mostly men, but this might be attributed to the male predominance of BrS.

### ***Sex-specific risk factors for arrhythmic events***

Risk stratification in BrS is difficult, particularly in women, because most data available are based on assessment of BrS men. Recently, studies with significant proportion of women with BrS have been published. A pooled analysis of three large studies suggests that women comprise nearly 28% of all BrS patients, although some patients may have been included in more than one registry.<sup>24-26</sup> One of these studies, a report on 1613 BrS patients (31% females), found fragmented QRS and QRS duration >120 ms to be significant predictors of arrhythmic events in female BrS patients (HR 20.2 and 4.7, respectively), incremental to common risk factors, such as proband status, history of syncope and sudden cardiac arrest (HR 10.15, 6.8 and 69.4, respectively).<sup>26</sup> These findings are particularly remarkable in the context of a recent study, which showed higher prevalence of *SCN5A* pathogenic variants in asymptomatic female BrS patients than males (27% vs 21%) and a further high prevalence in female BrS patients with arrhythmic events as compared to males (48% vs 28%),<sup>60</sup> suggesting that the presence of an *SCN5A* pathogenic variant in females may be a marker of higher arrhythmic risk. Additionally, an earlier study found longer PR intervals as an indicator of arrhythmic risk in female BrS patients despite similar PR durations in both sexes (HR 1.03 per each ms of increase).<sup>61</sup> Conduction disturbances are not uncommon in BrS patients and can be attributed to loss-of-function *SCN5A* variants, which underlie the most identifiable genetic forms of BrS and progressive cardiac conduction disease. Interestingly, certain *SCN5A* variants, such as Gly1406Arg, can produce a BrS phenotype in men and isolated conduction disease in women.<sup>62</sup>

Sinus node dysfunction (sinus bradycardia, sinus arrest, or junctional escape) occurs in 1% of men and women with BrS.<sup>26</sup> Interestingly, some familial BrS-associated *SCN5A* variants produce almost exclusively VF/SCD in men, but predominantly sick sinus syndrome and rarely VF/SCD in women.<sup>63</sup> Because VF in BrS patients is almost entirely during sleep, it has been proposed that arrhythmogenicity in BrS may be related to bradycardia resulting from increased vagal tone or other contributing factors. Thus, concomitant sinus node dysfunction could hypothetically increase the risk for an unfavorable outcome. While a previous study supported sinus node disease as an arrhythmia predictor in female BrS patients,<sup>24</sup> a recent analysis of a larger cohort refuted this association in a multivariate analysis model.<sup>26</sup> This highlights the need for refinement of BrS risk stratification, partly explained by the uncertainties regarding the mechanisms of arrhythmogenesis.

### ***Mechanisms underlying sex-related differences***

Two potential mechanisms of BrS are widely discussed in the literature: (1) depolarization disorder hypothesis, which suggests conduction delay in the right ventricular outflow tract (RVOT) as part of the mechanism of BrS, and is more supported by clinical data, and (2) repolarization disorder hypothesis, which is mainly based on evidence of non-uniform abbreviation of right ventricular epicardial action potentials in canine hearts (see [Figure 5](#) for details).<sup>64</sup> Accordingly, potential mechanisms underlying the striking sex-related disparities in BrS might be complex with the interplay of RVOT conduction slowing, differential ion channel expression in endocardium and epicardium, and non-uniform epicardial action potential shapes, which may create an arrhythmogenic milieu. Post-mortem histopathological examination and in vivo studies showed increased collagen in male BrS hearts compared to male controls.<sup>65</sup> In particular, male BrS patients were found to have epicardial surface and interstitial fibrosis and reduced gap junction expression in the RVOT.<sup>65</sup> Given the more predominant  $I_{to}$  in male right ventricular epicardium,<sup>66</sup> this might at least in part explain the male predominance of BrS.

Sex hormones have also been implicated in sex-related disparity in BrS. Male patients with BrS were found to have higher testosterone levels compared to controls.<sup>59</sup> In two men with spontaneous BrS, surgical castration for treatment of prostate cancer resulted in normalization of the ECG.<sup>67</sup> The modulatory role of testosterone on repolarization currents, namely  $I_{to}$  (increase) and  $I_{Ca,L}$  (decrease), and opposing effects by estrogen might contribute to sex-related differences in BrS ([Figure 5](#)).<sup>66</sup> Among these concepts, the effect of sex hormones may provide the most reasonable mechanistic explanation for the onset of phenotype distinction at puberty and its persistence until menopause.<sup>25</sup> However, data supporting these hypotheses is scarce, and the true pathobiology behind this variation is likely to involve an interplay of multiple contributing mechanisms.

Data from animal models of BrS on sex-related differences is scarce. The only study with findings potentially relevant for sex-associated differences in BrS reported that in mice with heterozygous deletion of *Scn5a*, more severe conduction slowing and cardiac fibrosis is observed in aged males compared to aged females, indicating a potential gender-specific impact on disease phenotype.

### ***Management***

Given the low risk of VF in asymptomatic patients with spontaneous BrS ECG ( $\approx 1\%$ /year), refraining from therapy is reasonable for well-informed patients.<sup>68</sup> All patients should receive aggressive and immediate treatment of fever and avoid drugs that may induce arrhythmias (list of drugs available at [www.brugadadrugs.org](http://www.brugadadrugs.org)). ICDs are recommended in patients with arrhythmic syncope and survivors of cardiac arrest.<sup>56</sup> The low risk for life-threatening arrhythmias (2% vs. 5% within 5 years of diagnosis) explains the lower rate of ICD implantation in women compared to men (20% vs. 34%).<sup>26</sup> Quinidine has been shown to prevent arrhythmic events in symptomatic BrS patients,<sup>69, 70</sup> and should be

considered in BrS patients with recurrent ventricular arrhythmias, atrial fibrillation or in those who choose to avoid an ICD.<sup>56</sup> Radiofrequency ablation of the arrhythmic substrate in the epicardium of the RVOT has mainly been investigated in male BrS patients and appears to reduce arrhythmias in BrS patients with recurrent VF episodes.<sup>71</sup>

### ***Pregnancy***

In a retrospective single-center study including 104 BrS women with 219 deliveries, not a single life-threatening arrhythmia was observed during the pregnancy or peripartum period.<sup>72</sup>

## **5. Catecholaminergic Polymorphic Ventricular Tachycardia**

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a cardiac channelopathy characterized by polymorphic ventricular arrhythmias in the setting of high adrenergic tone.<sup>73</sup> Pathogenic variants in the ryanodine receptor 2 gene (*RYR2*) are responsible for approximately 65% of CPVT cases, transmitted in an autosomal dominant manner, while variants in the cardiac calsequestrin gene (*CASQ2*), responsible for mainly an autosomal recessive form of the disease, are found in 2–5% of the CPVT cases.<sup>1</sup>

### ***Sex-related differences in clinical phenotype***

There appears to be a similar proportion of male and female CPVT cases ([Figure 3](#)).<sup>27</sup> Sex-related differences have been described in *RYR2*-CPVT, but appear to be minor. Although it was initially thought that males with *RYR2*-CPVT have a higher risk for SCD,<sup>74</sup> recent data do not support this association, and the risk of arrhythmias seems to be variant type/location-dependent. In a Canadian population, the founder *RyR2*-p.R420W variant significantly affected the survival in a sex-dependent manner, showing earlier mortality in males compared to females.<sup>75</sup>

A study aiming to evaluate the circadian variation of ventricular arrhythmias in pediatric CPVT cases revealed no difference in timing of arrhythmia events.<sup>76</sup>

### ***Sex-specific risk factors for arrhythmic events***

Large studies found no sex-specific risk factors for SCD in CPVT. The predictors for cardiac and fatal or near fatal events are younger age at the time of diagnosis and absence of  $\beta$ -blocker therapy.

### ***Management***

Currently, there are no sex-specific recommendations for management of CPVT patients.  $\beta$ -Blockers are the standard of care,<sup>1</sup> with nadolol being more beneficial than  $\beta_1$ -selective  $\beta$ -blockers. Recently, it was shown that flecainide added to  $\beta$ -blocker therapy is superior to  $\beta$ -blocker therapy alone for the prevention of exercise-induced arrhythmias in CPVT.<sup>77</sup> Left cardiac sympathetic denervation can be used for patients with drug intolerance or arrhythmias in spite of medical therapy. Although ICD is

currently recommended after cardiac arrest in CPVT,<sup>1</sup> recent data suggests that these may cause fatal VT storms, and strict adherence to medical therapy alone may be superior.<sup>78, 79</sup>

### ***Pregnancy***

A recent study showed that arrhythmic risk in CPVT patients is not elevated in the combined pregnancy and postpartum period. Events seen were associated with lack of  $\beta$ -blocker therapy and unrelated to pregnancy.<sup>80</sup> Thus, therapy with non-selective  $\beta$ -blockers should be continued throughout pregnancy and at least 40 weeks postpartum to alleviate the arrhythmic risk in CPVT patients.<sup>81</sup>

## **6. Short QT Syndrome**

Short-QT syndrome (SQTS) is a very rare, potentially lethal inherited channelopathy characterized by shortened QT interval (QTc <330ms) on ECG and increased susceptibility to atrial and ventricular arrhythmias and SCD.<sup>82</sup> The disease can also be diagnosed in the presence of a QTc <360 ms and one or more of the following: a pathogenic mutation, family history of SQTS, family history of sudden death at age  $\leq 40$ , survival of a VT/VF episode in the absence of heart disease.<sup>1</sup> SQTS1-3 are associated with gain-of-function variants in potassium channel genes (*KCNH2*, *KCNQ1*, and *KCNJ2*, respectively), whereas SQTS4-6 are caused by loss-of-function variants in calcium channel genes (*CACNA1C*, *CACNB2*, *CACNA2D1*, respectively).<sup>20</sup> SQTS patients may be asymptomatic or present with dizziness, syncope or SCD, often before the age of 40.<sup>82</sup>

Interestingly, there is a striking predominance of males (~70%) among patients with a clinical diagnosis of SQTS, suggesting a sex-dependent penetrance (Figure 3).<sup>28</sup> This may be because the resting QTc is longer in females than males, so that their QTc intervals are less likely to qualify for the diagnosis. There is, however, no sex-related difference in QTc duration among those diagnosed with SQTS.<sup>28, 82</sup> In a pooled analysis of available studies, male patients had a higher likelihood of syncope at first presentation (24% vs. 7%) with a similar risk of SCD compared to females (24% vs 25%).<sup>28</sup> A composite endpoint of VT, VF and SCD was more often observed in female (48%) than male patients (28%), perhaps partly due to higher detection rate of VT/VF in women, who all had ICDs implanted in contrast to only one third of males having an ICD.<sup>28</sup> Due to the low prevalence, our understanding of mechanisms responsible for these sex differences remains incomplete.

As there are no sex-specific risk factors for SCD, sex-specific recommendations for therapy do not exist. Because of the high rate of SCD in SQTS patients, ICD implantation is the cornerstone of therapy. ICD implantation is indicated in patients with sustained VT or VF, and can be considered in patients with a strong family history of SCD.<sup>1</sup> Quinidine has been shown to reduce the incidence of arrhythmias and might, therefore, be considered in asymptomatic patients with SQTS.<sup>83</sup> Sotalol may also be used for therapy, though less data supporting its efficacy is available.<sup>1</sup>

Studies on transgenic SQTs rabbit models, generated by overexpression of the human gain-of-function variant N588K in *HERG/KCNH2*,<sup>84</sup> showed a clear recapitulation of the human phenotype. No sex differences have been observed in QT duration, VT/VF-incidence or SCD rates.<sup>84</sup>

## 7. Sex-Related Differences in the Etiology and Risk of SADS

Sudden arrhythmic death syndrome (SADS) is defined as SCD in which both autopsy and toxicology investigations are inconclusive, the heart is structurally normal at gross and histological examination and non-cardiac etiologies are excluded.<sup>81</sup> The prevalence tends to be higher in younger victims. In a Canadian study of SCD victims aged  $\leq 19$  years, 60% had no identifiable cause of death.<sup>85</sup> In general, the prevalence is higher in men, with varying predominance in different age groups ([Figure 6](#)).<sup>86</sup> A study of 967 consecutive SADS cases showed a male predominance (61%) most evident in the younger age group.<sup>87</sup> The mean age was significantly lower in males ( $30 \pm 12.2$  years vs.  $33.5 \pm 15.4$  years). Circumstances of death were different between males and females. While the majority of SADS cases occurred during rest or sleep, male sex was more often associated with stress and exercise-related deaths.<sup>87</sup>

Clinical investigations of surviving relatives and post-mortem genetic testing are important tools in the diagnosis of an underlying genetic cause of many SADS cases, with a combined yield of up to 42%.<sup>86, 88</sup> Clinical evaluation often reveals various cardiac channelopathies, such as BrS (18-28%), LQTS (7%) and CPVT (2-10%).<sup>86, 88</sup> The higher risk of SCD in male children with LQTS and in adult males with BrS, as compared to females in the same age group might partly explain the higher incidence of SADS in men. Molecular autopsy in SADS has a reported yield of 13-32% depending on the population studies, the testing method and the thresholds for pathogenicity employed.<sup>86</sup> The subject's sex may also affect the diagnostic yield of the test. For example, a study of 173 SADS cases (38% female) referred for molecular autopsy showed a higher yield of pathogenic variant detection in females.<sup>89</sup> Among LQTS genotype-positive cases, 68% were female. In contrast, there was a higher proportion of males amongst *RYR2* (CPVT1) genotype-positive cases (55%) and they tended to be younger. This sex-age correlation of *RYR2* cases was confirmed in a later study.<sup>86</sup>

Little is known about sex differences among surviving family members of SADS subjects other than early data suggesting that more female relatives attended clinical evaluation than males,<sup>5</sup> and that following LQTS related deaths, the mothers are most likely to be the gene carrier.<sup>90</sup> This suggests that epigenetic factors such as imprinting may cause transmission distortion of LQTS genes.<sup>91, 92</sup>

## 8. General Considerations for Pregnant Women with Cardiac Channelopathies

Since cardiac channelopathies commonly manifest in adolescence or early adulthood, it is not

uncommon for physicians to deal with the challenge of pregnancy and the postpartum period in women with cardiac channelopathies. The current approach to pregnant women with a cardiac channelopathy includes identifying high-risk features, avoidance of arrhythmia triggers, preventive therapy when needed, and neonatal screening when possible. Between 5-10% of all sudden infant death syndrome cases are attributed to cardiac channelopathies.<sup>93</sup> In general infants are at low risk of cardiac events during infancy from channelopathies inherited from their parents, but should nonetheless be screened appropriately.

Unassisted vaginal delivery may be performed in women with cardiac channelopathies. It is, however, advisable to individualize the delivery plan according to the maternal risk profile; a history of arrhythmias should particularly be taken into account. In patients considered to be at high risk for malignant ventricular arrhythmias, availability of a cardiologist and/or electrophysiologist and maternal cardiac telemetry during labor are advisable. Anesthetic planning should include reviewing the list of medications that may potentially provoke arrhythmias to avoid drug-induced adverse reactions. For example, anesthetic drugs that prolong cardiac repolarization are strongly discouraged in LQTS patients.<sup>38</sup> In a series of 57 high-risk BrS patients undergoing ICD implantation, the injection of a single bolus propofol for induction of anesthesia was safe, with no adverse events noticed during the procedure or the recovery phase.<sup>94</sup> The authors however, cautioned about the potential of higher risk for BrS-related arrhythmias associated with the use of higher doses of propofol and longer infusions.<sup>94</sup>

Arrhythmic events during labour seem to be very rare. In some IAS, such as LQT1, LQT2 and CPVT, arrhythmias are more likely to be provoked by increased heart rate during exertion.<sup>1</sup> The highest heart rates during labor are observed in the active pushing phase. Notably, heart rate increases more in those receiving intravenous oxytocin. Moreover, oxytocin prolongs cardiac repolarization and can predispose LQTS patients to TdP arrhythmia, and should thus be used with caution during labor.

## **9. Conclusions**

Emerging data strongly support the presence of clinically relevant sex differences in the prevalence, risk profile and clinical course of several cardiac channelopathies. These differences likely result from a myriad of influences, extending from altered gene expression to hormonal effects, which, however, are insufficiently explored. Sex-specific neural stress response and psychosocial factors may also affect the outcome of cardiac channelopathies and warrant investigation. To address our current gaps in mechanistic understanding, awareness of biological sex as a modifier of cardiac channelopathy phenotype warrants further investigation. The sex-specific roles of steroid hormones on the expression and function of mutant cardiac ion channels needs to be evaluated in animal and human models. Epidemiological data on female and male patients at different ages is essential to understand how individual risk of life-threatening arrhythmias in different cardiac channelopathy genotypes varies over time. Attention should be paid to the incidence of arrhythmic events during phases of major hormonal



transitions (such as puberty, pregnancy, postpartum period, menopause) to refine our knowledge of hormonal influences on pathophysiology of cardiac channelopathies. Combining lessons learned from basic and clinical research may help target different pathogenic mechanisms to prevent fatalities at specific phases in life. Overall, recognition of sex-related differences in cardiac channelopathies along with improved mechanistic understanding of these disparities will likely translate into more personalized patient care, leading to improved clinical outcomes of patients with cardiac channelopathies.

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**Table 1.** The effects of sex hormones on cardiac electrophysiology and risk for sudden cardiac death.

Sex hormone	Effect on cardiac ionic currents					Change on ECG	Risk of SCD
	$I_{Ca,L}$	$I_{Ks}$	$I_{Kr}$	$I_{K1}$	$I_{to}$		
Estrogen	↑	↓	↓↑*	-	↓	↑QT interval	↓BrS and ↑LQTS
Progesterone <sup>†</sup>	↓	↑	-	-	-	↓QT interval	↓LQTS
Testosterone	↓↑‡	↑	↑	↑	↑	↓QT interval	↑BrS and ↓LQTS

\* Estrogen blocks the hERG channel ( $I_{Kr}$ ) directly, but conversely increases  $I_{Kr}$  via enhancing hERG membrane trafficking

† Progesterone here indicates endogenous progesterone.

‡ Testosterone acutely suppresses  $I_{Ca,L}$  directly, while in the long-term it activates nuclear receptor-mediated pathways for  $Ca_v1.2$  channel ( $I_{Ca,L}$ ) expression.

BrS = Brugada syndrome; ECG = electrocardiogram;  $I_{Ca,L}$  = L-type  $Ca^{2+}$  current;  $I_{Kr}$  = rapid component of the delayed rectifier  $K^+$  current;  $I_{Ks}$  = slow component of the delayed rectifier  $K^+$  current;  $I_{to}$  = cardiac transient outward  $K^+$  current;  $I_{K1}$  = inward rectifier  $K^+$  current.

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**Figure 1. Critical points to consider for management of patients with cardiac channelopathies.**

**Figure 2. Heart rate-corrected QT interval (QTc) distribution in health and disease.**

Modified from ref. <sup>6</sup> with permission.

**Figure 3. Approximate sex distribution of patients diagnosed with cardiac channelopathies.**

For LQTS, proportions are based on the report of Kutuyifa et al.<sup>23</sup>, which included only genetically confirmed LQTS cases from the Rochester-based Long QT syndrome registry. For BrS, proportions represent the average of reports by Sieira et al.,<sup>24</sup> Milman et al.,<sup>25</sup> and Berthome et al.<sup>26</sup> The diagnosis of BrS in these studies was made according to the criteria defined in the international guidelines.<sup>1</sup> For CPVT, proportions are based on the report by Roston et al.<sup>27</sup> The diagnosis of CPVT in this study was made according to the criteria defined in the international guidelines.<sup>1</sup> For SQTs, proportions are based on the meta-analysis of all short QT syndrome cases by El-Battrawy et al.<sup>28</sup>

BrS, Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; LQTS, long QT syndrome; SQTs, short QT syndrome.

**Figure 4. Schematic representation of the complex interplay of factors that determine the sex-related differences in cardiac channelopathies.**

**A.** The genetic components that contribute to the phenotype of cardiac channelopathies include sex chromosomes, genetic variation (single-nucleotide polymorphisms [SNPs] and copy number variants [CNVs]) and de novo variants. **B.** Sex-related differences can exist in the DNA accessibility and methylation status because of different epigenetic modification patterns. **C.** Sex-specific differences exist in the levels and patterns of gene expression. Regulation of cardiac ion-channel gene expression by sex hormones is one example. For simplified presentation, only the effects of estrogen are shown. **D.** Differences in exposure to exogenous factors such as physical activity, food products, medications and dietary supplements can contribute to the sex-related differences in cardiac channelopathies. **E.** Sex hormones have significant direct and indirect influence on cardiac electrophysiology in healthy humans as well as in patients affected by cardiac channelopathies. Female and male sex hormones can enhance or alleviate the arrhythmogenic potential at different ages and reproductive phases.

FSH, follicle-stimulating hormone; GPER, G-protein-coupled estrogen receptor; LH, luteinizing hormone.

**Figure 5. Schematic representation of proposed mechanisms underlying Brugada syndrome.**

**A.** Depolarization disorder hypothesis. According to this hypothesis, the Brugada ECG pattern results from conduction delay in right ventricular outflow tract (RVOT) with respect to the right ventricle (RV). During the hatched phase of the cardiac cycle, the membrane potential in RV is more positive than in RVOT, driving intercellular current to RVOT (upper panel, a). In a closed-loop circuit, current

passes back from RVOT to RV in the extracellular space (upper panel, c), and an ECG electrode positioned over the RVOT ( $V_{2IC3}$ ) inscribes a positive signal (bold red line), as it records the limb of this closed-circuit which travels towards it (upper panel, b). Reciprocal events are recorded in the left precordial leads; current flowing from the extracellular space into RV (upper panel, d) causes ST depression. Following the upstroke of the delayed AP in RVOT, the potential gradients between RV and RVOT are reversed, as membrane potentials are now more positive in RVOT than RV; this drives the closed-loop circuit in the opposite direction (lower panel), with current now passing away from lead  $V_{2IC3}$  (lower panel, d), thus resulting in the negative T wave (lower panel, bold blue line). When RV and RVOT are electrically well-coupled, the delayed AP of RVOT is abbreviated in comparison to RV AP; this accelerates repolarization of RVOT AP (the mass of RV strongly exceeding that of RVOT).

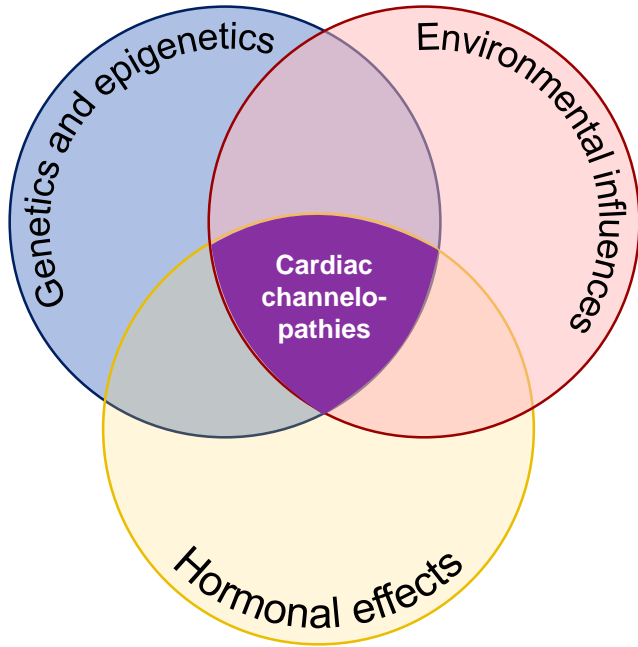
B. Differences between the epicardial and endocardial APs of RV/RVOT in healthy hearts, and AP changes underlining the ECG manifestation of Brugada syndrome (lower panel). The repolarization disorder hypothesis of Brugada syndrome evolves around the higher expression of  $I_{to}$  in epicardium than in endocardium. Since  $I_{to}$  is responsible for the early repolarization, stronger  $I_{to}$  in the epicardium than in endocardium renders epicardium susceptible to the effects of reduced depolarizing force. Hence, when  $I_{Na}$  is reduced due to  $Na^+$  channel variants, a “spike-and-dome” shape of the action potential (AP) arises in the epicardium. Prolongation of epicardial AP dome leads to longer AP durations in the epicardium than in the endocardium, which accounts for the negative T-wave on surface ECG. With further  $I_{Na}$  reduction,  $I_{to}$  repolarizes the membrane beyond the voltage at which L-type  $Ca^{2+}$  channels ( $I_{Ca,L}$ ) are activated, resulting in heterogeneous loss of the AP dome in the epicardium. Epicardial dispersion of repolarization results in vulnerability to premature impulses (phase 2 reentry), which can trigger ventricular arrhythmias based on reentry between transmural layers.<sup>64</sup>

The unaltered AP shape in endocardium in spite of  $I_{Na}$  reduction, a prerequisite for this hypothesis, is explained by less  $I_{to}$  expression in the endocardium. The presence of ECG changes in only right precordial leads results from larger  $I_{to}$  expression in the right ventricular than left ventricular epicardium, whereas the higher disease prevalence in men is explained by higher epicardial  $I_{to}$  density in males.

**Figure 6. Distribution of sudden arrhythmic death syndrome cases among age groups in males and females.**

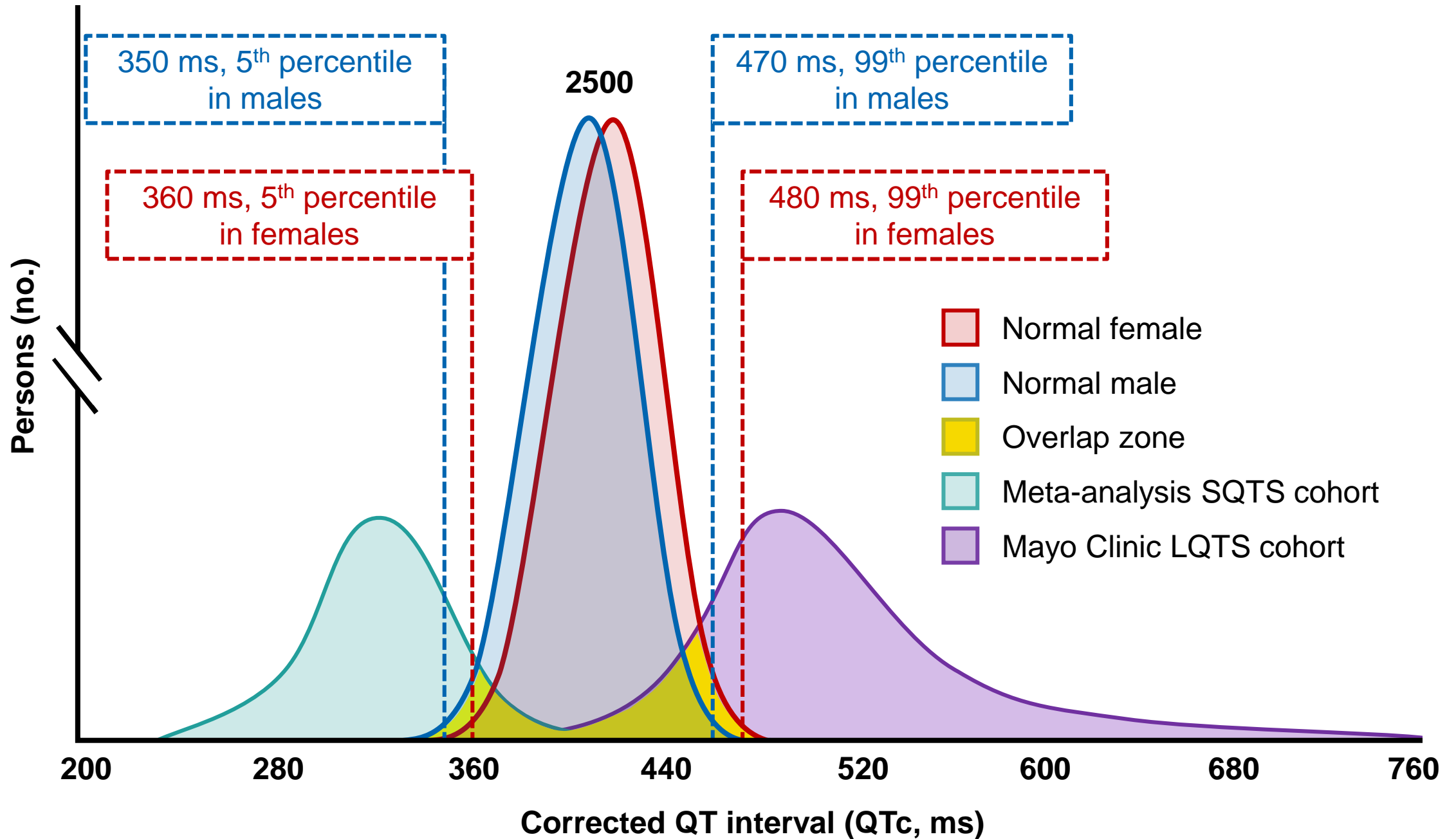
Comprehensive post-mortem investigation of a large cohort of 302 sudden arrhythmic death syndrome (SADS) cases revealed that SADS more often affected males and individuals 35 years and younger. The heights of the bars and the counts inside the bars represent the number of cases; the percentages represent the proportion of SADS cases in the respective group in the overall cohort of SADS cases.

Reproduced from ref.<sup>86</sup>.

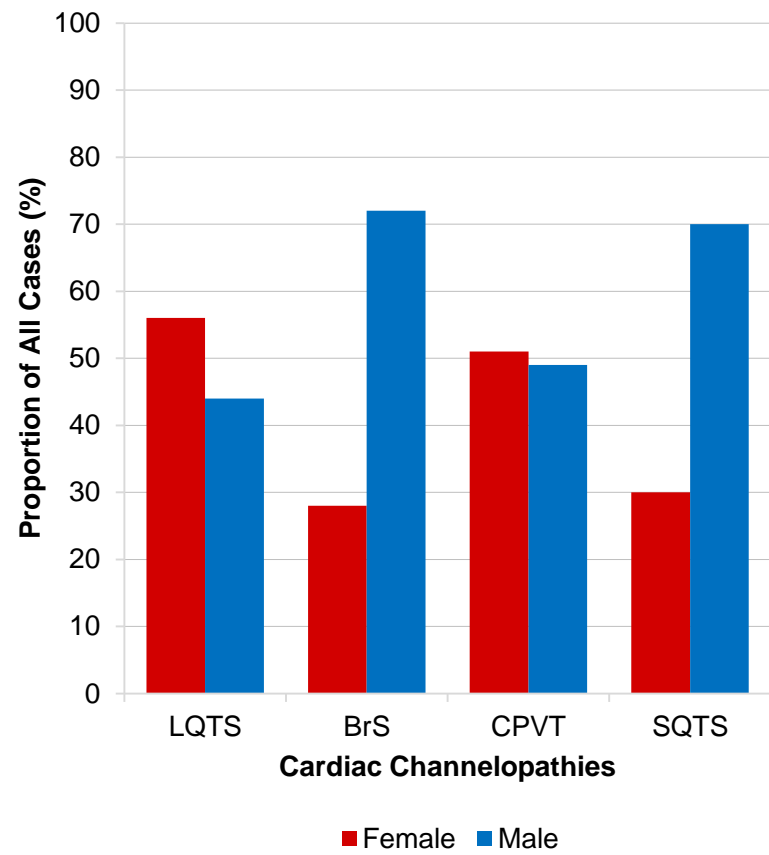


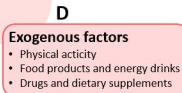
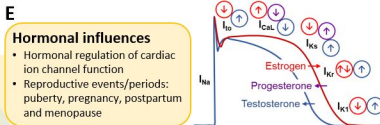
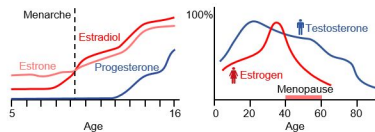
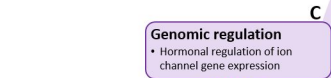
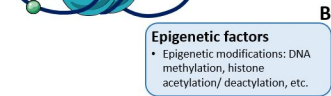
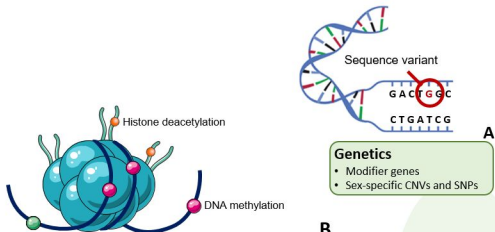
## Critical points to consider for management of patients with cardiac channelopathies:

- Disease-specific ECG features
- Sex-specific risk factors
- Age at the time of diagnosis
- History of palpitations, (pre)syncope, or ventricular arrhythmias
- Family history of cardiac channelopathy, sudden cardiac arrest/death
- Extent and level of physical activity
- Use of medications, food products, and dietary supplements









Physical activity

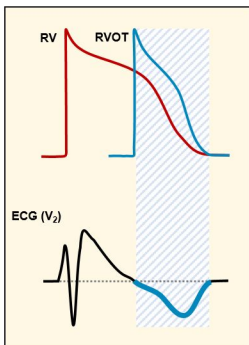
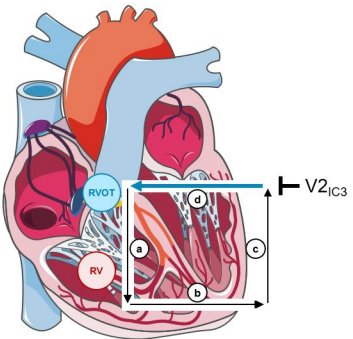
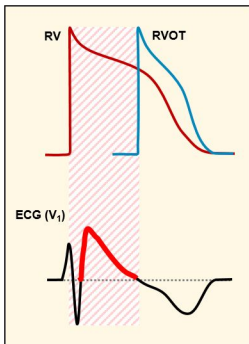
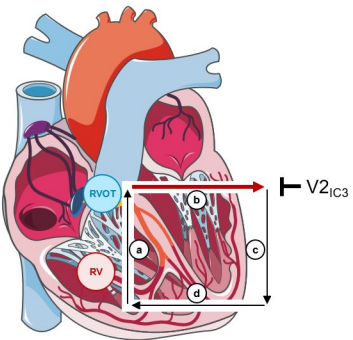


Food products and energy drinks

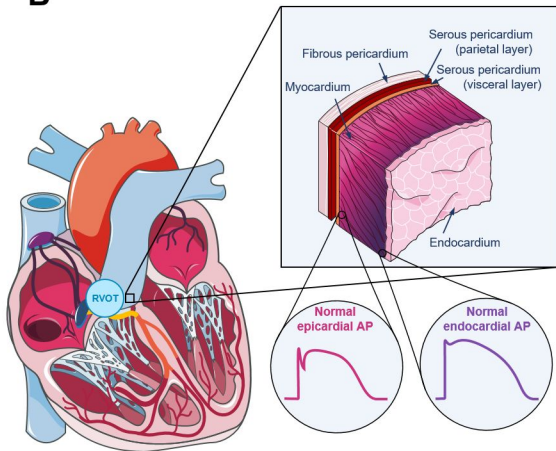


Drugs and dietary supplements

## A Brugada syndrome depolarization disorder hypothesis



## B Healthy heart



## Brugada syndrome repolarization disorder hypothesis

