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WOMEN AND HEART DISEASE (C. LINDE, SECTION EDITOR)

Prevalence, Clinical Presentation, and Management of Channelopathies and Cardiomyopathies, Long QT Syndrome, Brugada Syndrome, Arrhythmogenic Cardiomyopathy, and Hypertrophic Cardiomyopathy

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Abstract

Purpose of Review With this paper, we aim to summarize the knowledge on gender differences in the most common inheritable channelopathies and cardiomyopathies, focusing on aspects that are of clinical importance for patient management and follow-up.

Recent Findings Despite autosomal dominant inheritance patterns in most of the inheritable cardiac channelopathies and cardiomyopathies, there is increasing awareness that there are important gender differences in disease penetrance and severity, affecting prevalence, clinical presentation, and patient management.

Summary Important gender differences are present in Long QT syndrome, Brugada syndrome, arrhythmogenic cardiomyopathy, and hypertrophic cardiomyopathy. In LQTS, genotype-specific differences are important, and female LQT2 patients have higher arrhythmic risk compared with male. In the remaining inheritable channelopathies and cardiomyopathies discussed in this review, male patients are more likely to have penetrant disease and experience arrhythmic events. Mechanistic explanations for the observed gender differences are sparse, but in channelopathies, hormonal effects are thought to be important. Although treatment strategies in inheritable channelopathies and cardiomyopathies are similar in men and women with the notable exception of women with LQT2, the differences between the sexes are important to be aware of in patient management.

Keywords Long QT syndrome · Brugada syndrome · Arrhythmogenic cardiomyopathy · Hypertrophic cardiomyopathy · Gender differences · Sex differences

Introduction

Despite autosomal dominant inheritance patterns in most of the inheritable cardiac channelopathies and cardiomyopathies, there are important gender differences in disease penetrance and severity, affecting prevalence, clinical presentation, and patient management. These gender differences are important to acknowledge when working with patients with long QT syndrome (LQTS), Brugada syndrome, arrhythmogenic cardiomyopathy (AC, former arrhytmogenic right ventricular cardiomyopathy (ARVC)), and hypertrophic cardiomyopathy (HCM), particularly regarding risk stratification of ventricular arrhythmias. The hormonal effects on different ion channels may partly explain the sex differences observed in LQTS and Brugada syndrome, whereas in AC and HCM mechanisms for these differences are less well described and are likely multifactorial.

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Congenital Long QT Syndrome

Prevalence and Clinical Presentation

Long QT syndrome (LQTS) is characterized by prolonged QT interval on ECG (Fig. 1) and a propensity for malignant

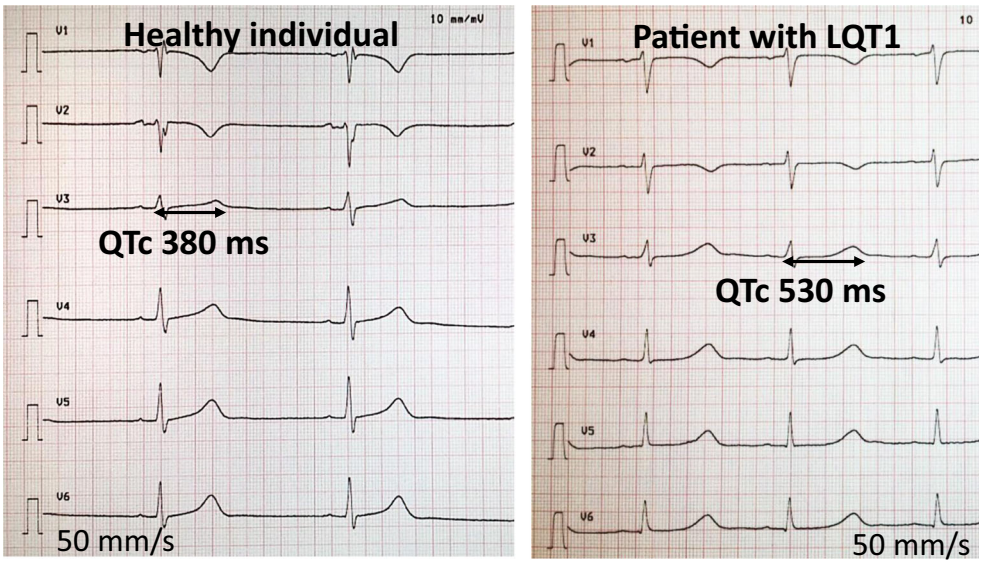

Fig. 1 EGC from a healthy individual (left) and an LQTS patient (right). The QT interval is severely increased in the LQTS patient

ventricular arrhythmias, syncope, and sudden cardiac death. The QT interval is heart rate–dependent, and therefore the heart rate–corrected QTc, calculated by, e.g., Bazett's formula as QT interval/√RR-interval, is used for diagnosis. LQTS is the best described ion channelopathy, and sex differences are well known and differ between the specific genetic subtypes.

The QT interval is physiologically longer in women than in men, and previously recommended cutoff values for prolonged QT interval differed between men (QTc > 450 ms) and women (QTc > 460 ms). However, the latest guidelines propose a QTc > 480 ms in the absence of secondary causes for QTc prolongation, to diagnose LQTS for both sexes [1•], while a QTc of 460 ms is sufficient to make a diagnosis in the presence of unexplained syncope [1•].

Genetically determined LQTS has an estimated prevalence of 1:2000 [2]. Mutations in genes encoding ion channel subunits have been found in 60–75% of clinically diagnosed LQTS patients [3, 4], and in total, 15 genes have been shown to be associated with the autosomal dominant form (Romano Ward syndrome) and 2 genes with the autosomal recessive subtype (Jervell-Lange Nielsen Syndrome) [5]. Jervell-Lange Nielsen syndrome is characterized by congenital, sensorineural deafness in addition to a severe cardiac phenotype [6, 7].

Importantly, there are significant sex differences in disease penetrance and severity which have to be acknowledged in patient management.

LQT1

Mutations in the KCNQ1-gene cause defect IKs potassium channels with a phenotype of LQT1, which is the most common form of LQTS. IKs is most important for normal repolarization when heart rate increases, and arrhythmic events are typically triggered by exercise.

Young boys with LQT1 have higher risk of ventricular arrhythmias and fatal events compared with girls carrying the same mutation. However, in puberty, the risk of arrhythmias is lower in males than females [8]. Therefore, if there have been no arrhythmic events until the age of 16, the risk of arrhythmias in males decreases, while in females, it remains the same or increases [8, 9].

LQT2

The sex differences are most obvious in LQT2. Mutations in the KCNH2 gene cause defect IKr potassium channels, which is the most important potassium channel for repolarization at rest. Arrhythmias are typically triggered by emotions and loud noises. Throughout the lifespan, the risk of arrhythmias is higher in females compared with males [8, 10]. Therefore, women with LQT2 and QTc > 500 ms are considered at higher risk than men with similar findings, and should be evaluated for primary preventive ICD [1•, 11]. Interestingly, in LQT2 women, the risk of arrhythmias remains increased also after menopause, suggesting lifelong follow-up and therapy [12].

In LQT2 women, the risk of arrhythmias increases significantly in the post-partum period, persisting for the first 9–12 months after delivery [13]. Beta blocker therapy should, therefore, be continued during pregnancy and under no circumstances be reduced in the post-partum period [13]. Management of mothers with LQT2 could also include information that nightly nursing may be handled by the father to ensure adequate rest for the mother, as sleep deprivation is a risk factor for arrhythmic events [14]. A home automatic external defibrillator or a wearable defibrillator may be an option in mothers as a bridge during the post-partum period when ICD is not indicated or not preferred although this is not included in current guidelines.

LQT3

LQT3 is caused by mutations in the SCN5A gene encoding the late sodium channel. Arrhythmic events are typically elicited by rest or sleep. LQT3 children seem to have lower risk of events compared with LQT2 and LQT1 children, but risk increases in adulthood [8]. However, if arrhythmic events occur in childhood, they are likely to become life-threatening, and LQT3 is believed to be a contributor to sudden infant death syndrome [15]. There are conflicting reports on sex differences in the risk of ventricular arrhythmias in LQT3. One study indicated higher arrhythmic risk in LQT3 men [16], while others found no difference in the risk of arrhythmic events between the genders [8]. Beta blocker efficacy to prevent ventricular arrhythmia may be more effective in women with LQT3 compared with men [17].

Hormonal Differences and Arrhythmic Risk

In animal studies using transgenic LQT2 rabbits, estradiol exerted a pro-arrhythmic effect, while progesterone exerted an anti-arrhythmic, protective effect [18]. In patients with acquired LQTS, drug-induced QT prolongation is more pronounced and the risk for drug-induced arrhythmias is higher during menses and the follicular phase (with high estradiol serum levels) than during the luteal phase (with relatively higher progesterone levels) [19]. These observations suggest a pro-arrhythmic role for estradiol and an anti-arrhythmic effect of progesterone in humans [20], although there are no large studies on arrhythmias and menstrual cycles in women with congenital LQTS.

Management

Beta blocker treatment is recommended in all clinically diagnosed LQTS patients (Class I B), and should also be considered in asymptomatic, mutation-positive family members (Class IIa B) [1•]. These recommendations apply to both men and women, but as discussed above, special attention should be payed to LQT2 women, and in particular in the post-partum period. The genotype should be evaluated as part of the risk stratification, as there is a higher recurrence of symptoms during beta blocker treatment in LQT2 compared with LQT1 [14].

Regardless of gender, ICD implantation is recommended in survivors of cardiac arrest (Class I B) and should be considered if symptoms persist despite beta blocker treatment (Class IIa) [1•]. If available, left cardiac sympathetic denervation should be considered if there are contraindications against beta blockers or ICD, or in case of breakthrough symptoms on beta blocker therapy (Class IIa) [1•].

Brugada Syndrome

Prevalence and Clinical Presentation

Brugada syndrome is clinically characterized by ventricular arrhythmias causing syncope or sudden cardiac death, typically occurring during sleep or rest. Fever, excessive alcohol intake, and large meals are known to increase the risk of arrhythmic events. The diagnosis is based on the finding of a type 1 Brugada ECG pattern consisting of a right bundle branch block pattern and ST segment elevation, either spontaneously or after administrations of a sodium channel blocker [1•]. However, fluctuating ECG patterns make the diagnosis difficult.

Mutations are found in approximately 30% of clinically diagnosed cases, and more than 20 different genes have been shown to cause Brugada syndrome, of which the SCN5A gene encoding the late sodium channel is the most common and most important [1•]. The inheritance pattern is thought to be autosomal dominant with incomplete penetrance. Prevalence is estimated at between 1:1000 and 1:10000 in different continents, and the disease seems to be more prevalent in South East Asia.

Gender Differences

Brugada syndrome has well described sex differences with greater symptoms and event rates and more frequently spontaneous type 1 ECG in post-pubertal male patients [21, 22]. There is no full mechanistic understanding of the observed sex differences, but it has been suggested that androgens may affect the I_{to} channel and aggravate ion channel dysfunction. Hormonal effects on the Brugada phenotype would also explain the regression of the typical ECG features in castrated men [23]. The effects of oestrogens in Brugada syndrome are less well known. However, pregnancy and the peri-partum period seem to be well tolerated in women with Brugada syndrome [24]. Whether the risk of arrhythmias changes in postmenopausal women is unknown.

Management

ICD is the only treatment strategy shown to increase survival [1•]. The main challenge is to choose which patients would benefit from an ICD. The latest guidelines state that a diagnostic ECG and an aborted cardiac arrest or a documented sustained VT should warrant an ICD implantation [1•]. However, they also argue that it is not indicated in asymptomatic subjects with a type 1 ECG, even with a family history of sudden cardiac death. Treatment strategies are similar in both sexes, but as more male patients experience symptoms, men are more likely to be implanted with an ICD. Quinidine and isoproterenol may be considered, particularly during arrhythmic storms, although no larger studies have shown anti-arrhythmic effects. Aggressive treatment of fever and lifestyle

changes such as avoiding large alcohol intakes are also important, as well as avoiding drugs thought to increase the susceptibility to arrhythmias (brugadadrugs.org).

Arrhythmogenic Cardiomyopathy

Prevalence and Clinical Presentation

Arrhythmogenic cardiomyopathy (AC) (former arrhythmogenic right ventricular cardiomyopathy, ARVC) is clinically characterized by exercise-induced syncope or sudden cardiac death and is an important cause of death in young individuals and athletes in particular. Patients may present with symptoms of heart failure, but arrhythmic debut is more common. The diagnosis is based on Task Force Criteria [25], including the evaluation of the presence of ventricular arrhythmias, typical morpho-functional changes, ECG-changes, tissue characterization, and family history resulting in a diagnosis of definite, borderline, or possible AC. The morpho-functional criteria include parameters from echocardiography and cardiac magnetic resonance imaging which should be performed as part of the diagnostic work-up. AC is a progressive cardiomyopathy with a gradual fibro-fatty replacement of cardiomyocytes. In the early "concealed phase," individuals are often asymptomatic, but are at risk of ventricular arrhythmias and sudden cardiac death. In the overt "electrical phase," individuals present with symptomatic arrhythmias, and right and more rarely left, ventricular morphological abnormalities may or may not be detectable by conventional imaging modalities. Finally, diffuse, progressive disease may result in right, left, or biventricular heart failure, often combined with ventricular arrhythmias.

Genetics

Genetic AC has an autosomal dominant inheritance pattern, with incomplete penetrance. Mutations are found in approximately 50% [26] of patients, and desomosomal genes are most commonly involved, including Desmoplakin (DSP), plakoglobin (JUP), plakophilin-2 (PKP2), desmocollin 2 (DSC2), and desmoglein-2 (DSG2). It is important to notice that high levels of genetic noise and age-related and variable penetrance warrant cautious interpretation of genetic findings.

Gender Differences

Prevalence of AC is estimated to be 1:1000–1:5000 [1•]. Penetrance is incomplete, but cardiac penetrance is reported to be threefold higher in men compared with women [27]. Men are also more frequently probands and are more severely affected, and male sex has been reported as a risk factor for ventricular arrhythmias [28•], but studies are inconsistent. The reasons for the higher penetrance and arrhythmic risk in men are not clear. It is known that athletic activity has a major impact on disease severity and progression [29, 30], and higher frequency of male athletes may be one of the potential explanations.

Management

Imaging parameters for AC diagnosis are adjusted for body surface area (BSA) [31•], but otherwise, no sex-specific differences in diagnostic criteria or management of AC patients are established. Treatment strategies [1•] include a recommendation for avoidance of competitive sports, and maximally tolerated dosages of beta blockers. However, in an observational registry, beta blockers including sotalol did not seem to reduce ventricular arrhythmias [32]. ICD implantation is recommended in patients with an aborted cardiac arrest, and should be considered in patients with documented, well-tolerated, sustained VT and in high risk individuals.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is defined as increased left ventricular wall thickness that is not solely explained by abnormal loading conditions. It is the most common genetic cardiomyopathy, with an estimated prevalence of 1:500 [26]. The disease is typically asymptomatic at early stages, but patients have increased risk of arrhythmias resulting in syncope or even sudden cardiac death. Furthermore, the hypertrophy may cause obstruction of the left ventricular outflow tract, resulting in the development of heart failure. Mutations were found in approximately 50–60% of patients [26], most typically in sarcomere protein genes, including the beta-myosin heavy chain gene (MYH7), the cardiac myosin binding protein c gene (MYBPC3), the troponin T gene, and the alpha-tropomyocin gene.

Gender Differences

In HCM, penetrance of disease is higher in men [1•, 33], and a 3:2 ratio in male versus female patients has been reported [34]. Consequently, women are more frequently asymptomatic mutation carriers compared with men. Importantly, the risk of ventricular arrhythmias in women with penetrant HCM is at least equal to the risk in men [34]. Therefore, in women with HCM, arrhythmic risk should not be falsely underestimated, and sex should not be considered in risk stratification for ventricular arrhythmias in patients with overt HCM. Women are also reported to be older at diagnosis, more frequently symptomatic and at higher risk for death from heart failure or stroke compared with men [34]. These gender-specific differences suggest that social, endocrine, genetic, or other factors may affect the diagnosis and clinical course of HCM.

Management

Patients with HCM are at considerable arrhythmic risk, and treatment strategies are similar in both sexes [1•]. Avoidance of competitive sports has been recommended in patients with manifest disease, especially if a left ventricular outflow tract (LVOT) gradient is present. In recent reports, the avoidance of exercise is less strict and suggests that exercise may be beneficial [35•, 36•]. There is little evidence for the benefit of using anti-arrhythmic medications in HCM patients. Amiodarone possibly reduces the incidence of SCD in patients with documented non-sustained ventricular tachycardia, but this finding is not consistent. Disopyramide and beta blockers are used to treat LVOT obstruction, but there is no evidence that they reduce the risk of SCD. Surgical myectomy or septal alcohol ablation is used to treat patients with high LVOT gradients, but is not recommended to reduce risk of SCD even in patients with LVOT obstruction. The main treatment question in terms of reducing risk of sudden cardiac death is choosing the patients would benefit from an ICD. The latest European Guidelines [1•] recommend using the HCM risk-SCD calculator to evaluate arrhythmic risk and include recommended cut of values for annual risk of SCD that should warrant ICD implantation. The predictor variables used in the model are all associated with an increased risk of SCD in at least one published multivariable analysis. Sex differences are not included in risk stratification.

Conclusions

There are important gender differences in all the channelopathies and cardiomyopathies we have discussed in this review. Mechanistic explanations are sparse, but in channelopathies, hormonal effects are thought to be important. In LQTS, there are genotype-specific differences which are important to be aware of in patient management. Young boys with LQT1 have higher risk of ventricular arrhythmias and fatal events compared with girls carrying the same mutation, but this risk ratio changes in puberty. In LQT2, the lifespan risk of arrhythmias is higher in females compared with males, with the postpartum period being the most susceptible period. With the exception of LQTS, male patients with inheritable channelopathies and cardiomyopathies are more likely to have penetrant disease and experience arrhythmic events: In the Brugada syndrome, male patients are more frequently symptomatic and have higher event rates. Also, in AC, cardiac penetrance is reported to be threefold higher in men compared with women, and some studies report male sex as a risk factor for ventricular arrhythmias. Similarly, in HCM, disease penetrance is higher in male patients, and consequently, women are more frequently asymptomatic mutation carriers. Importantly, the risk of ventricular arrhythmias in women with penetrant HCM is at least equal to the risk in men, and therefore gender should not be included in arrhythmic risk stratification in symptomatic HCM patients. In inheritable channelopathies and cardiomyopathies, treatment strategies are mostly similar in men and women, with the notable exception of women with LQT2, but even so, the differences between the sexes are important to be aware of in patient management.

Compliance with Ethical Standards

Conflict of Interest Ida S. Leren and Kristina H. Haugaa declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.• Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015;36(41):2793–867. https://doi.org/10.1093/eurheartj/ehv316. **Important guideline paper on sudden cardiac death, including channelopathies and cardiomyopathies**.
2. Schwartz PJ, Stramba-Badiale M, Crotti L, Pedrazzini M, Besana A, Bosi G, et al. Prevalence of the congenital long-QT syndrome. Circulation. 2009;120(18):1761–7. https://doi.org/10.1161/circulationaha.109.863209.
3. Napolitano C, Priori SG, Schwartz PJ, Bloise R, Ronchetti E, Nastoli J, et al. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. JAMA : the journal of the American Medical Association. 2005;294(23):2975–80. https://doi.org/10.1001/jama.294.23.2975.
4. Zareba W. Genotype-specific ECG patterns in long QT syndrome. J Electrocardiol. 2006;39(4 Suppl):S101–6. https://doi.org/10.1016/j.jelectrocard.2006.05.017.
5. Nakano Y, Shimizu W. Genetics of long-QT syndrome. J Hum Genet. 2015;61:51–5. https://doi.org/10.1038/jhg.2015.74.
6. Jervell A, Lange-Nielsen F. Congenital deaf-mutism, functional heart disease with prolongation of the Q-T interval and sudden death. Am Heart J. 1957;54(1):59–68.
7. Crotti L, Celano G, Dagradi F, Schwartz PJ. Congenital long QT syndrome. Orphanet J Rare Dis. 2008;3:18. https://doi.org/10.1186/1750-1172-3-18.
8. Zareba W, Moss AJ, Locati EH, Lehmann MH, Peterson DR, Hall WJ, et al. Modulating effects of age and gender on the clinical course of long QT syndrome by genotype. J Am Coll Cardiol. 2003;42(1):103–9.

9. Sauer AJ, Moss AJ, McNitt S, Peterson DR, Zareba W, Robinson JL, et al. Long QT syndrome in adults. J Am Coll Cardiol. 2007;49(3):329–37. https://doi.org/10.1016/j.jacc.2006.08.057.
10. Migdalovich D, Moss AJ, Lopes CM, Costa J, Ouellet G, Barsheshet A, et al. Mutation and gender-specific risk in type 2 long QT syndrome: implications for risk stratification for life-threatening cardiac events in patients with long QT syndrome. Heart Rhythm. 2011;8(10):1537–43. https://doi.org/10.1016/j.hrthm.2011.03.049.
11. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes. Heart Rhythm. 2013;10(12):e85–108. https://doi.org/10.1016/j.hrthm.2013.07.021.
12. Buber J, Mathew J, Moss AJ, Hall WJ, Barsheshet A, McNitt S, et al. Risk of recurrent cardiac events after onset of menopause in women with congenital long-QT syndrome types 1 and 2. Circulation. 2011;123(24):2784–91. https://doi.org/10.1161/circulationaha.110.000620.
13. Seth R, Moss AJ, McNitt S, Zareba W, Andrews ML, Qi M, et al. Long QT syndrome and pregnancy. J Am Coll Cardiol. 2007;49(10):1092–8. https://doi.org/10.1016/j.jacc.2006.09.054.
14. Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. Circulation. 2001;103(1):89–95.
15. Arnestad M, Crotti L, Rognum TO, Insolia R, Pedrazzini M, Ferrandi C, et al. Prevalence of long-QT syndrome gene variants in sudden infant death syndrome. Circulation. 2007;115(3):361–7. https://doi.org/10.1161/circulationaha.106.658021.
16. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, et al. Risk stratification in the long-QT syndrome. N Engl J Med. 2003;348(19):1866–74. https://doi.org/10.1056/NEJMoa022147.
17. Wilde AA, Moss AJ, Kaufman ES, Shimizu W, Peterson DR, Benhorin J, et al. Clinical aspects of type 3 long-QT syndrome: an international multicenter study. Circulation. 2016;134(12):872–82. https://doi.org/10.1161/circulationaha.116.021823.
18. Odening KE, Choi BR, Liu GX, Hartmann K, Ziv O, Chaves L, et al. Estradiol promotes sudden cardiac death in transgenic long QT type 2 rabbits while progesterone is protective. Heart Rhythm. 2012;9(5):823–32. https://doi.org/10.1016/j.hrthm.2012.01.009.
19. Rodriguez I, Kilborn MJ, Liu XK, Pezzullo JC, Woosley RL. Drug-induced QT prolongation in women during the menstrual cycle. JAMA : the journal of the American Medical Association. 2001;285(10):1322–6.
20. Odening KE, Koren G. How do sex hormones modify arrhythmogenesis in long QT syndrome? Sex hormone effects on arrhythmogenic substrate and triggered activity. Heart Rhythm. 2014;11(11):2107–15. https://doi.org/10.1016/j.hrthm.2014.06.023.
21. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, et al. Long-term prognosis of patients diagnosed with Brugada syndrome: results from the FINGER Brugada syndrome registry. Circulation. 2010;121(5):635–43. https://doi.org/10.1161/circulationaha.109.887026.
22. Benito B, Sarkozy A, Mont L, Henkens S, Berruezo A, Tamborero D, et al. Gender differences in clinical manifestations of Brugada syndrome. J Am Coll Cardiol. 2008;52(19):1567–73. https://doi.org/10.1016/j.jacc.2008.07.052.
23. Matsuo K, Akahoshi M, Seto S, Yano K. Disappearance of the Brugada-type electrocardiogram after surgical castration: a role for testosterone and an explanation for the male preponderance. Pacing Clin Electrophysiol. 2003;26(7 Pt 1):1551–3.
24. Rodriguez-Manero M, Casado-Arroyo R, Sarkozy A, Leysen E, Sieira JA, Namdar M, et al. The clinical significance of pregnancy in Brugada syndrome. Rev Esp Cardiol (English ed). 2014;67(3):176–80. https://doi.org/10.1016/j.rec.2013.06.023.
25. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. Eur Heart J. 2010;31(7):806–14. https://doi.org/10.1093/eurheartj/ehq025.
26. Ackerman MJ, Priori SG, Willems S, Berul C, Brugada R, Calkins H, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies: this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Europace: European pacing, arrhythmias, and cardiac electrophysiology: journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2011;13(8):1077–109. https://doi.org/10.1093/europace/eur245.
27. Bauce B, Frigo G, Marcus FI, Basso C, Rampazzo A, Maddalena F, et al. Comparison of clinical features of arrhythmogenic right ventricular cardiomyopathy in men versus women. Am J Cardiol. 2008;102(9):1252–7. https://doi.org/10.1016/j.amjcard.2008.06.054.
28.• Corrado D, Wichter T, Link MS, Hauer R, Marchlinski F, Anastasakis A, et al. Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement. Eur Heart J. 2015;36(46):3227–37. https://doi.org/10.1093/eurheartj/ehv162. **A comprehensive overview of risk assessment in arrhythmogenic right ventricular cardiomyopathy**.
29. Saberniak J, Hasselberg NE, Borgquist R, Platonov PG, Sarvari SI, Smith HJ, et al. Vigorous physical activity impairs myocardial function in patients with arrhythmogenic right ventricular cardiomyopathy and in mutation positive family members. Eur J Heart Fail. 2014;16(12):1337–44. https://doi.org/10.1002/ejhf.181.
30. James CA, Bhonsale A, Tichnell C, Murray B, Russell SD, Tandri H, et al. Exercise increases age-related penetrance and arrhythmic risk in arrhythmogenic right ventricular dysplasia/cardiomyopathy-associated desmosomal mutation carriers. J Am Coll Cardiol. 2013;62(14):1290–7. https://doi.org/10.1016/j.jacc.2013.06.033.
31.• Haugaa KH, Basso C, Badano LP, Bucciarelli-Ducci C, Cardim N, Gaemperli O, et al. Comprehensive multi-modality imaging approach in arrhythmogenic cardiomyopathy—an expert consensus document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2017;18:237–53. https://doi.org/10.1093/ehjci/jew229. **A comprehensive overview of imaging for diagnosis and risk assessment in arrhythmogenic right ventricular cardiomyopathy**.
32. Marcus GM, Glidden DV, Polonsky B, Zareba W, Smith LM, Cannom DS, et al. Efficacy of antiarrhythmic drugs in arrhythmogenic right ventricular cardiomyopathy: a report from the North American ARVC Registry. J Am Coll Cardiol. 2009;54(7):609–15. https://doi.org/10.1016/j.jacc.2009.04.052.
33. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(39):2733–79. https://doi.org/10.1093/eurheartj/ehu284.

34. Olivotto I, Maron MS, Adabag AS, Casey SA, Vargiu D, Link MS, et al. Gender-related differences in the clinical presentation and outcome of hypertrophic cardiomyopathy. J Am Coll Cardiol. 2005;46(3):480–7. https://doi.org/10.1016/j.jacc.2005.04.043.

35.• Dejgaard LA, Haland TF, Lie OH, Ribe M, Bjune T, Leren IS, et al. Vigorous exercise in patients with hypertrophic cardiomyopathy. Int J Cardiol. 2018;250:157–63. https://doi.org/10.1016/j.ijcard.2017.07.015. **Important data on exercise in hypertrophic cardiomyopathy indicating no harm of long time exercise**.

36.• Saberi S, Wheeler M, Bragg-Gresham J, Hornsby W, Agarwal PP, Attili A, et al. Effect of moderate-intensity exercise training on peak oxygen consumption in patients with hypertrophic cardiomyopathy: a randomized clinical trial. JAMA. 2017;317(13):1349–57. https://doi.org/10.1001/jama.2017.2503. **Important data on exercise in hypertrophic cardiomyopathy indicating no harm of long time exercise**.