ESC European Society of Cardiology

Europace (2018) **20**, 1565
doi:10.1093/europace/euy067

EHRA POSITION PAPER

Sex differences in cardiac arrhythmia: a consensus document of the European Heart Rhythm Association, endorsed by the Heart Rhythm Society and Asia Pacific Heart Rhythm Society

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Online publish-ahead-of-print 28 June 2018

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Keywords Sex • Gender • Female • Women • Arrhythmia • Atrial arrhythmias • Atrial fibrillation • Ventricular arrhythmias • Sudden death • Stroke • Thromboembolism • Epidemiology • Cardiac implantable electronic devices • Implantable cardioverter-defibrillators • Pacemakers • Cardiac resynchronization therapy • Ablation • European Heart Rhythm Association consensus document • European Heart Rhythm Association position paper

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Introduction

Preamble/definitions

There is an increasing awareness that sex is a major determinant of the incidence, aetiology, and clinical presentation of arrhythmias, and that there are sex differences in access and response to arrhythmia therapies. Women traditionally were under-represented in the clinical trials but trial results have been extrapolated to the female population assuming identical results in men and women. Insufficient knowledge of physiology, epidemiology, and treatment outcome in women have led to lack of sex-specific recommendations and under-utilization of existing guideline-based therapies, in women.[1] One of the very few guidelines where sex and gender differences were addressed is the 2016 ESC guidelines on the management of atrial fibrillation (AF).[2] In this document, it was stated as Class I recommendation that 'AF clinicians must offer effective diagnostic tools and therapeutic management to women and men equally to prevent stroke and death'. In our document, we would like to continue this initiative and expand similar recommendations to other type of cardiac arrhythmias but emphasizing when evidence calls for equal management and when the evidence is insufficient which in turn is a call for further studies. The aim of this consensus document is to provide an overview of sex differences in the pathophysiology, epidemiology,

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and management of cardiac arrhythmias, to highlight factors limiting the access to contemporary therapies, and to develop the pathways that may improve quality of medical care in women with cardiac arrhythmias. Suggestions for the design of future clinical trials in women are also provided.

Definition of sex and gender

In many previous publications on the differences between women and men, the terms 'sex' and 'gender' have been used almost interchangeably. While both these terms have distinct meanings, they are not synonyms.

The term 'sex' is used to indicate the presence of biological differences between female and male individuals, which in homo sapiens (similar to most other mammals) corresponds to the distinction between XX and XY sex chromosomes. By contrast, 'gender' is primarily a grammatical term (distinguishing masculine, feminine, and neutral nouns in Latin and many other languages) that is also used to denote cultural and societal distinction in prevalent and/or expected roles of women and men in a given cultural environment.

Consequently, in this document, we will use the terms 'sex' and 'gender' to distinguish between biologically and cultural differences between women and men, realising that some of the differences described further might be a combination of both. For instance, if the lower participation of women in clinical trials were contributed by their being biologically more prone to avoid risk and the unexpected, this difference is would be based on sex. If, on the contrary, researchers running clinical trials were less willing to enrol women because they perceived them as more demanding and likely to be lost on follow-up, their decision would be based on gender. The terms sex- and gender-discrimination are also being used interchangeably but we should also employ them separately along the same lines. Medical gender-discrimination (hopefully rare) would include depriving women of appropriate treatment because they were perceived to be less worth the expense. Sex-discrimination in modern medicine includes applying to women stratification limits (e.g. those for the QRS complex width) derived from studies conducted predominantly in men, despite the knowledge of biological sex differences.

Evidence review

Members of the Task Force were asked to perform a detailed literature review, weigh the strength of evidence for or against a particular treatment (or procedure), and include estimates of expected health outcomes where data existed. Patient-specific modifiers, comorbidities, and issues of patient preference that might influence the choice of particular tests or therapies are considered, as are frequency of follow-up and cost effectiveness. In controversial areas, or with regard to issues without evidence other than usual clinical practice, a consensus was achieved by agreement of the expert panel after thorough discussions. This document was prepared by the Task Force with representation from European Heart Rhythm Association (EHRA), Heart Rhythm Society (HRS), and Asia-Pacific Heart Rhythm Society (APHRS). The document was peer-reviewed by official external reviewers representing EHRA, HRS, and APHRS.

Grading

Consensus statements are evidence-based, and derived primarily from published data. Current systems of ranking level of evidence are becoming complicated in a way that their practical utility might be compromised. We have, therefore, opted for an easier and, perhaps, more user-friendly system of ranking that should allow physicians to easily assess current status of evidence and consequent guidance (*Table 1*).

Thus, a 'green heart' indicates a recommended statement or recommended/indicated treatment (or procedure) and is based on at least one randomized trial, or is supported by large observational evidence that it is beneficial and effective. A 'yellow heart' indicates general agreement and/or scientific evidence favouring a statement or the usefulness/efficacy of a treatment or procedure. A yellow heart may be supported by randomized trials based on small number of patients or not widely applicable. Treatment strategies for which there has been scientific evidence that they are potentially harmful and should not be used are indicated by a 'red heart'.

It may be added that regarding this document a 'green heart' rarely can be given for women due to lack of evidence. We were thus unable to use green for most recommendations because robust evidence is not available which is a 'call for action'. To 'lower' the level of evidence required to support the use of treatment/diagnostics in women would be regressive rather than progressive.[3] EHRA grading of consensus statements does not have separate definitions of level of evidence. The categorization used for consensus statements (used in consensus documents) should not be considered as being directly similar to that used for official society guideline recommendations which apply a classification (I–III) and level of evidence (A, B, and C) to recommendations in official guidelines. Finally, this is a consensus document that includes evidence and expert opinions from several

Table 1 Scientific rationale of recommendations

Definitions where related to a treatment or procedure	Consensus statement	Symbol
Scientific evidence that treatment or procedure is beneficial and effective. Requires at least one randomized trial, or is supported by strong observational evidence and authors' consensus	Recommended/ indicated	
General agreement and/or scientific evidence favour usefulness/ efficacy of treatment or procedure. May be supported by randomized trials based on small number of patients or not widely applicable	May be used or recommended	
Scientific evidence or general agreement not to use or recommend treatment or procedure	Should NOT be used or recommended	

This categorization of our consensus document should not be considered as being directly similar to that used for official society guideline recommendations which apply a classification (I–III) and level of evidence (A, B, and C) to recommendations.

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countries. Some drug therapies may not be approved by governmental regulatory agencies in all countries.

Industry relationship

It is EHRA and ESC policy to sponsor position papers and guidelines without commercial support, and all members volunteered their time. Thus, all members of the writing group as well as reviewers have disclosed any potential conflict of interest in detail, at the end of this document.

Sex differences in cellular electrophysiology and surface electrocardiogram

Cellular and tissue electrophysiology

The myocardial action potential by trans-membrane ionic currents is relatively well understood. Sex differences in several of these currents and in their regulation have been described but the comparisons of different studies are not necessarily conclusive. Moreover, for some experimental findings in cardiomyocytes and cardiac tissue, the possibility of intra-species differences needs to be considered.

Depolarising sodium currents have been described to be less homogeneously distributed across the ventricular wall of female canine hearts with the regional disparities decreased by testosterone.[4] On the contrary, larger differences in late sodium currents were observed between left and right atrial myocytes in male rabbits compared with females.[5] There is more consistency in studies examining sex differences in excitation-contraction coupling.[6] Contractions of female ventricular myocytes appear smaller and slower in females compared with male cells, particularly at faster pacing rates. Whilst myocyte Ca^{2+} current density is similar in both sexes, cell shortening and Ca^{2+} transients were smaller in females and Ca^{2+} transients were smaller in female cells.[7] But in another study in guinea pig heart peak L-type Ca(2+) current (*I*(CaL)) was larger in females suggesting that sex differences in action-potential duration (APD) result from variation in the kinetics of *I*(CaL) stemming from alterations to Ca(2+) release.[8]

Reasonably consistent agreement also exists on sex differences of myocardial repolarization. Action-potential duration of female myocytes is longer than that of male cells paced at the same slow rate[9,10] while the difference in APD practically disappeared in the presence of isoproterenol. Blocking Ca^{2+}-release from the sarcoplasmic reticulum had a larger impact on isoproterenol-induced changes in female compared with male myocytes.[10] It has also been suggested the sex difference of myocardial repolarization is contributed by the differences in Ca^{2+}-handling.[8] Female cells have also been reported to show increased susceptibility to early after depolarizations, thus perhaps contributing to reduced repolarization reserve.[11,12]

Studies of the direct effects of sex hormones on repolarization ion channels have not been conclusive. Nevertheless, greater dispersion of Ca^{2+}-currents was described in female animal hearts and attributed to the effects of sex hormones.[13] This led to the suggestions that effects of sex hormones are the mechanisms that make females more susceptible to drug-induced torsades de pointes tachycardia and to sudden death in the congenital long QT syndrome (LQTS) further described in Management of Supraventricular Ectopies and Paroxysmal Supraventricular Tachycardia section.

Key points

Established beyond reasonable doubt	
Consistent findings	• Female and male ventricular myocytes appear to differ with respect to size and kinetics of the Ca^{2+} currents • At slow pacing rates, APD of female myocytes is longer than that of male cells
Plausible findings	• Sex hormones influence Ca^{2+} currents • Potassium currents differ in female and male cardiomyocytes[a]

[a]See Effects of sex hormones section.

Electrocardiography

The physiological normal electrocardiogram (ECG) shows many sex differences. The amplitude of the P- and T-waves and width of the QRS complex are lower in women than in men because of smaller organ sizes and possibly the larger layer of breast tissue between the heart and the ECG electrodes.[14] Electrocardiogram recording noise also appears to be larger in women, probably also because of the recordings being technically influenced by the electrical properties of the breast tissue. The background of many of these differences is unknown. It is well established that compared with men, women have ST segments with a shallower slope and a less steep ascent of the T-wave[15] although the clinical implications of this finding are unknown.

With regard to intra-cardiac cardiac conduction, women tend to have shorter PR intervals,[13] shorter AH- and HV-intervals, shorter effective refractory period of the atrioventricular (AV) node,[16] and slightly narrower QRS complex[17,18] with possibly slightly greater differences at faster heart rates (*Figure 1*). While women generally have smaller hearts, the difference in physiological intra-ventricular conduction times does not seem to be explainable only by the organ size[19,20] (*Figure 2*). Nevertheless, the proportion of apparently healthy women who show prolonged QRS complex at faster heart rate is the same as in apparently healthy men. In addition, there are also race differences. Similar to men, women of African origin have been reported to have shorter QRS duration compared with Caucasian women.[20]

Many of the known sex differences in normal ECG concern repolarization although the physiological background of many of these differences is unknown. For a long time, it has been known (although with little clinical implications) that compared with men, women have ST segments with a shallower slope and a less steep ascent of the T-wave.[15]

The QT interval duration, is approximately 20 ms longer in women than in men at resting heart rates.[21] Although the majority of studies were based on Bazett's correction which overestimates this difference because of the faster resting heart rate in women, the difference

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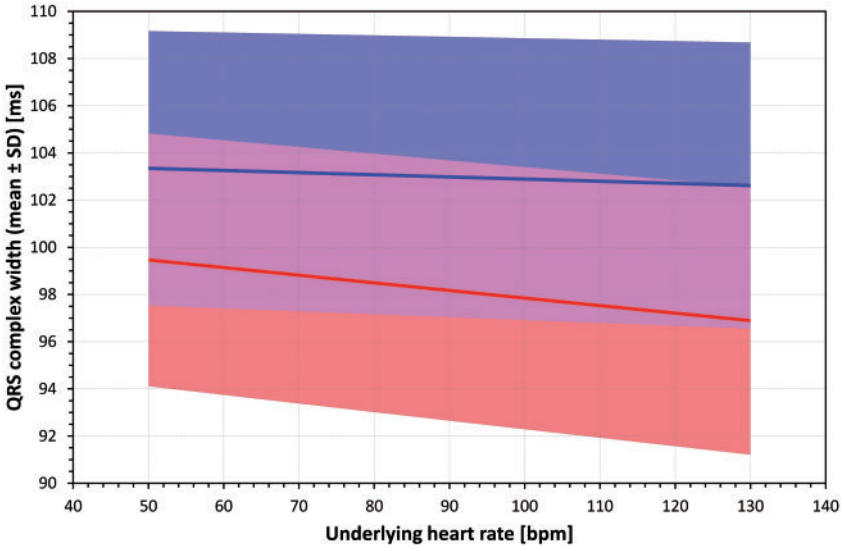

Figure 1 Interpolated population dependency of the QRS width on underlying heart rate in women and men. The graphs are based on approximately 500 000 verified ECG measurements in 176 healthy females and males aged 18–55 years. Redrawn from Ref.[20] Lines and bands represent mean ± SD. The red line with the pink band shows the data in women, the blue line with the aquamarine band shows the data in men. The violet area shows the overlap of the ±SD bands of both sexes. Note that the sex differences are in single ms and that they marginally increase with increasing heart rate. b.p.m., beats per minute; SD, standard deviation.

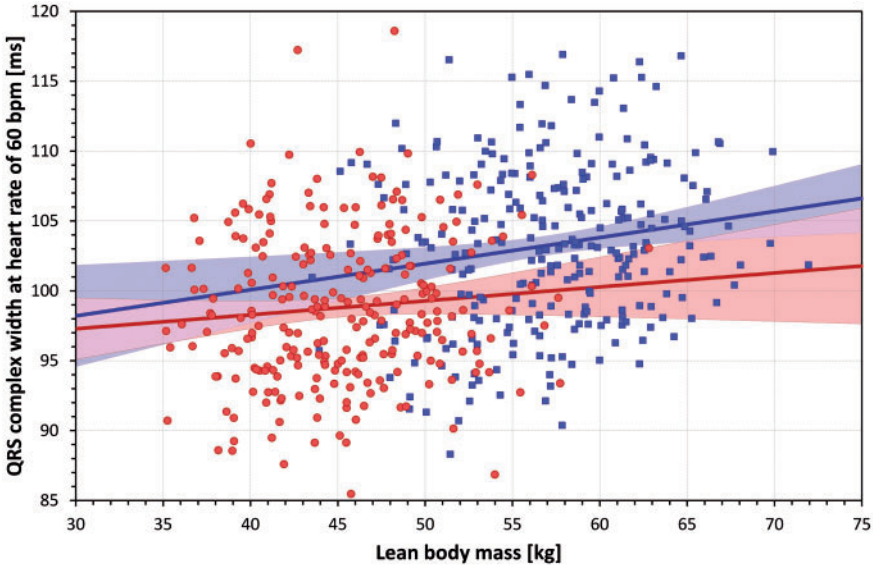

Figure 2 Scatter diagram of QRS width measured at heart rate of 60 b.p.m. vs. lean body mass (for approximate heart size comparisons) in a population of 254 pre-menopausal adult women (red circles) and 269 correspondingly aged men (blue squares). Redrawn from data presented in Ref.[20] The data of women and men are shown as red circles and blue squares, respectively. The regression lines are shown with a red line and a pink 95% confidence interval for women, and a blue line with an aquamarine confidence interval for men. The violet areas show the overlaps of the confidence intervals of both sexes. Note that while women have smaller bodies (and thus also smaller hearts) the difference between QRS durations is independently of these body size differences. b.p.m., beats per minute.

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exists independent of this correction inaccuracy. Consistent with the cellular and tissue electrophysiology, QT interval in women is likely caused by the effects of sex hormones.[22] There is little difference in the QTc interval between pre-puberty girls and boys[21,23] and in the elderly, the sex difference seems attenuated[24] (*Figure 3*).

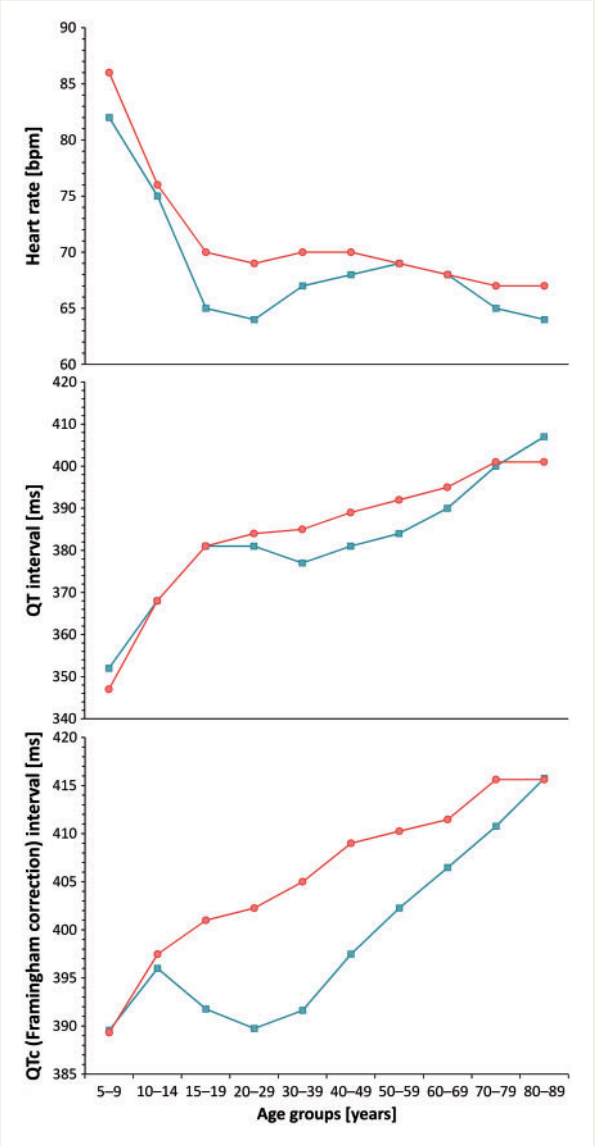

Figure 3 Mean values of heart rates (top panel) and of uncorrected QT intervals (middle panel) published by *Rautaharju et al.*[24] for a population of broad age ranges. The bottom panel shows QTc (Framingham study correction) derived from the mean values. The data for women and men are shown in red and blue, respectively. Note that while in women, the data suggest gradual increase of QTc with advancing age; men show post-pubertal dip with gradual return to increasing QTc values similar to women. Nevertheless, this evaluation is based on the assumption that the same QT/heart rate relationship can be used for QTc correction not only for both sexes but also for different age groups. Both these assumptions are likely substantial oversimplifications. b.p.m., beats per minute; QTc, rate corrected QT interval.

Nevertheless, since sex differences exist in both heart rate and uncorrected QTc interval, the sex and age difference in rate corrected QTc is also influenced by the QT/heart rate relationship (which is likely influenced by autonomic decline with advancing age). QTc intervals in heart transplant recipients in whom the sex of the donor and of the recipient differ appear to maintain the QTc difference associated with the sex of the recipients[25] suggesting that sex hormones play an important role in determining the QTc interval duration.

The relationship of QT interval to heart rate is not only steeper in women, diminishing the sex difference at fast heart rates (*Figure 4*) but also, when assessed on individual basis, more curved in women compared with men.[26] Studies of QT/RR hysteresis show that women appear to adapt the QT interval to changing heart rates slightly faster than men.[26] Women also have narrower spatial angle between the vectorcardiographic loops of the QRS complex and of the T-wave. Although the angle increases with increasing heart rate in both women and men the sex difference also appears to increase with increasing rate (*Figure 4*).[27] As an increased spatial QRS-T angle signifies an increased risk in many cardiac populations, different criteria for women and men need to be considered.

In studies of drug-induced repolarization changes, women tend to have larger QTc response to drugs blocking the delayed potassium rectifier current such as e.g. amiodarone, propafenon, and dronedarone. However, these differences appear to be explained by lower body weights in women compared with men and thus increased plasma concentrations when the investigated drug is administered at the same doses in both sexes.[28] Only occasional studies described steeper slope of QTc response to drug concentration in women.[29] The differences in electrophysiological properties between women and men are summarized in *Figure 5*.[30]

Key points

Established beyond reasonable doubt	• At slow baseline heart rates, pre-menopausal adult women have longer QTc intervals than men of corresponding ages
Consistent findings	• The QTc difference between pre-menopausal women and men of similar age diminishes with increasing heart rate • Women have marginally shorter QRS complex than men • Women have steeper individual QT/RR profiles • Women have larger spatial difference between QRS and T-wave loop orientations
Plausible findings	• Pre-menopausal adult women have increased ventricular repolarization heterogeneity compared with similarly aged men • After adjusting for plasma concentration differences, QTc responses to drugs blocking the delayed potassium rectifier current are similar in women and men

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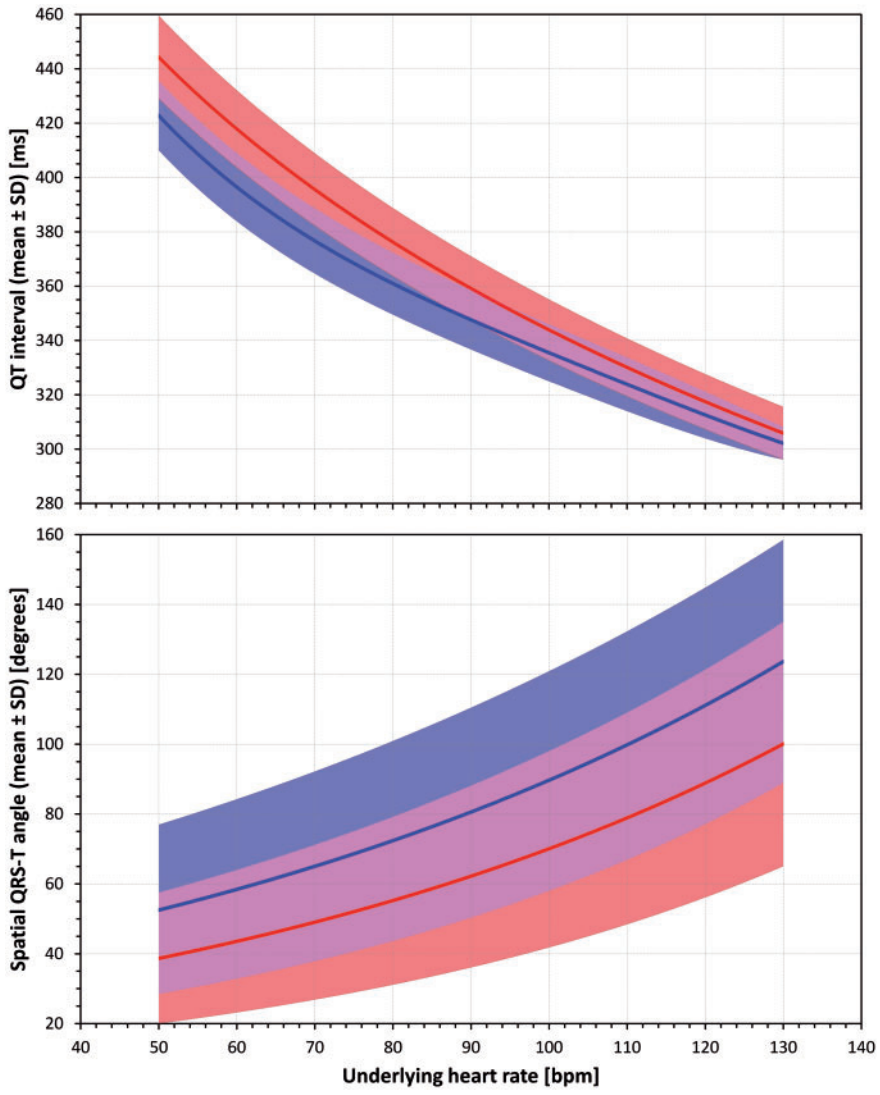

Figure 4 Interpolated population dependency of QT interval (upper panel), PR interval (middle panel) and of spatial QRS-T angles (lower panel) on underlying heart rate in pre-menopausal women and correspondingly aged men. The graphs are based on approximately 500 000 verified ECG measurements in 176 healthy females and 176 healthy males aged 18–55 years. Redrawn from data presented in Ref.[26] The red lines with pink bands show the data in women, the blue lines with aquamarine bands show the data in men. Mean± SD are shown. The violet shaded area shows the overlap of the ±SD bands. Note that with both parameters, the sex difference depends on the underlying heart rate. b.p.m., beats per minute; SD, standard deviation.

Cardiac autonomic regulation

Autonomic regulation plays an important role in arrhythmogenesis.[31] Sex differences in cardiac autonomic status and in cardiovascular (CV) autonomic reflexes, therefore, also need to be considered. Pre-menopausal adult women have faster heart rates than men.[24] The difference to men again appears to be related to sex hormones since there is neither significant difference[24] between female and male foetal heart rates[32] nor significant heart rate difference between girls and boys until puberty.[21] The exact onset of the heart rate differences between sexes is disputable but women have consistently higher heart rates than age matched males between the ages of 20 to about 50 years. After middle age, this difference gradually diminishes and eventually disappears mostly because of a heart rate decline in females.[33] Compared with men, spectral analyses of heart rate variability in women have reported an increase in high-frequency components that are associated with vagal modulation of the sinoatrial node.[34] The ratio between the low-frequency and high-frequency components, expressing the sympathovagal balance, is consequently lower in women. In both sexes, the heart rate variability decreases with advancing age. Little data exists on autonomic responses to standardized provocations, but it seems that sympathetically active challenges lead to larger autonomic shifts in women. Strong sympathetic inputs may even abolish the sex difference altogether. The extent to which these larger sympathetic changes contribute to different

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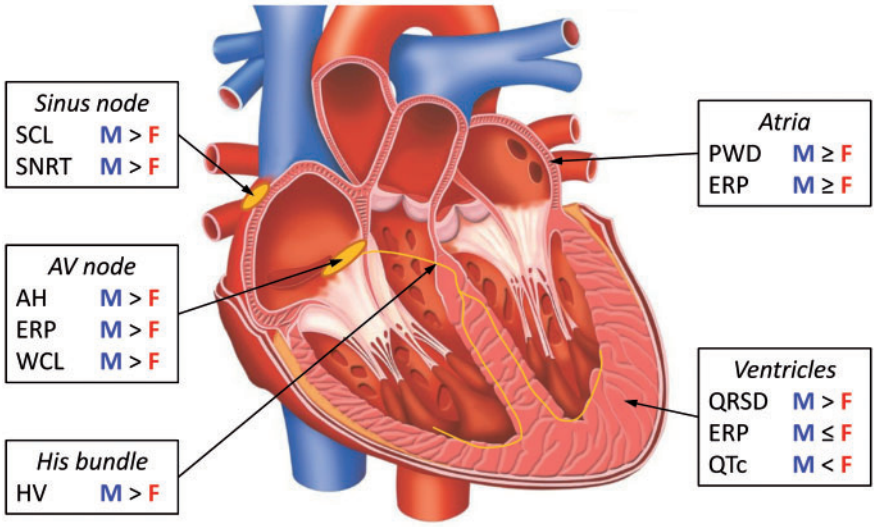

Figure 5 Sex differences in the normal electrophysiological variables. Left side shows properties of the electrically active tissues, right side of the contractile myocardium. ≥, longer; ≤, shorter; AH, AH interval; AV, atrioventricular; ERP, effective refractory period; F, female; HV, HV interval; M, male; PWD, P-wave duration; QRSD, QRS complex duration; QTc, QTc interval; SCL, sinus cycle length; SNRT, sinus node recovery time; WCL, Wenckebach cycle lenght. Redrawn with permission from Tadros *et al.*[30]

arrhythmia susceptibility is not known. Nevertheless, baroreflex sensitivity, reported indicator of the strength of antiarrhythmic autonomic defence, has been found lower in middle-aged women than men.[34] After autonomic blockade, no gender differences in sinus nodal properties were noted, whereas AV nodal refractoriness and conduction time became shorter in women, and QT- and JT-duration and the refractory period of the right ventricle were shorter in men. In another study, vagal activation was more common in women than in men during abrupt coronary occlusion which may have beneficial antiarrhythmic effects, modifying the outcome of acute coronary events in women.[35]

In conclusion, these differences may be reason for AV nodal re-entry tachycardia and acquired LQT are more commonly seen in women and why women in the setting of ischaemia in women experience less ventricular tachyarrhythmia than men.

Key points

Established beyond reasonable doubt	• Compared with men of similar ages, pre-menopausal adult women have faster baseline heart rates
Consistent findings	• Compared with men of similar ages, pre-menopausal adult women have larger vagally modulated RR period variations
Plausible findings	• During autonomic challenges, the sympathovagal differences are suppressed between pre-menopausal adult women and correspondingly aged men

Effects of sex hormones

Sex differences in ventricular repolarization involve effects of sex hormones through differences in expression of ion channel subunits and channel function modulation.[30] Female hearts have reduced expression of potassium channel subunits involved in cardiac repolarization, including HERG, minK, Kir2.3, Kv1.4, KChIP2, SUR2, and Kir6.2.[12] In addition, sex hormones influence these channels differently. Oestradiol inhibits I_{Kr}. In contrast, testosterone increases I_{Ks}, herewith exhibiting a protective arrhythmic influence.[36] In rabbits treated with quinidine plus either oestradiol or dihydroxytestosterone, respectively, the oestradiol-treated rabbits experienced significantly more QTc prolongation.[37] Second, sex hormones not only affect APD but also the expression and function of calcium cyclic proteins that are involved in generating early after depolarizations and triggered activity in this way setting the stage for arrhythmias.[36] Underlying mechanism also may include a larger peak L-type Ca^{2+} current (I_{CaL}) in females.[9,30] In other words, the effects of sex on the risk of arrhythmias go beyond their effects on APD alone.

During the menstrual cycle, levels of oestrogen and progesterone reflect the follicular and luteal phase. A number of studies linked the hormonal changes during the cycle to changes in cardiac electrophysiology and cardiac autonomic status. While, as described in subsequent sections, these changes have implications for arrhythmia risk and arrhythmia incidence, the results of the different studies have been largely inconclusive and many of the observations have not been reproduced. For instance, while one study described shortened QTc interval during the luteal than the follicular phase[38] other studies reported no differences.[39,40] Similar disagreements exist on other electrophysiological and autonomic measurements. Thus, while female sex hormones seem to be of only of minor influence on duration and distribution of ventricular repolarization, testosterone

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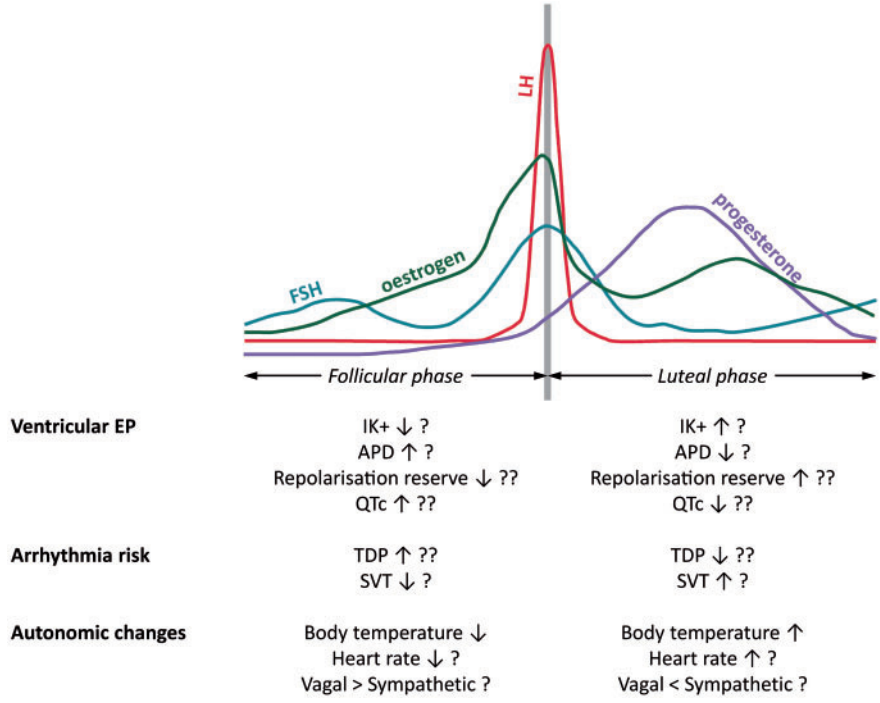

Figure 6 Observed and speculative changes during menstrual cycle. Question marks and double question marks indicate previously questioned and questionable observations, respectively. APD, action-potential duration; EP, electrophysiology; FSH, Follicle-stimulating hormone; IK+, delayed potassium rectifier currents; LH, Luteinizing hormone; QTc, rate corrected QT interval; SVT, supraventricular tachycardia; TDP, torsade de pointes. Redrawn with permission from Tadros *et al.*[30]

seems to play a major role in determining both the QT interval duration and the susceptibility to repolarization-related tachyarrhythmias.[24] Some of the speculations that have been reported on the effects of menstrual cycle on ventricular electrophysiology and cardiac autonomic status are summarized in *Figure 6*. A detailed discussion of frequently controversial findings has also been published in Ref.[41]

Prevalence, clinical presentation, and management of channelopathies and cardiomyopathies

There are specific sex differences in patients with channelopathies that are important to take into consideration when managing patients with these diseases and for risk stratification of ventricular arrhythmias. Despite the autosomal dominant inheritance, affecting men and women equally, there are important differences in disease penetrance and severity. The hormonal effects on different ion channels partly explain the sex differences observed in LQTS and Brugada syndrome as explained in Sex Differences in Cellular Electrophysiology and Surface Electrocardiograms and Prevalence, Clinical Presentation, and Management of Chanellopathies and Cardiomyopathies sections, while hormonal effects are less clear in catecholaminergic polymorphic ventricular tachycardia (CPVT) and in idiopathic ventricular fibrillation (VF). There are also sex differences in cardiomyopathies, such as arrhythmogenic cardiomyopathy (ARVC) and hypertrophic cardiomyopathy (HCM), while the mechanisms for these differences are less well described and may be multifactorial.

Channelopathies

Congenital long QT syndrome

Long QT syndrome is the best described ion channelopathy. It has a pathophysiological explanation model ranging from the genetic mutation to the clinical symptoms. The sex differences explained by the hormonal effects on defect ion channels have also been clarified. The QT interval is physiologically longer in women than in men (see Sex Differences in Cellular Electrophysiology and Surface Electrocardiograms section) and a prolonged QT-interval has previously been defined with different cut-off values in women (QTc >460 ms) and in men (QTc >450 ms). However, recent guidelines propose a QTc >480 ms to diagnose LQTS for both sexes[42] while a QTc ≥460 ms is sufficient to make a diagnosis in the presence of unexplained syncope.[42]

Mutations in the KCNQ1-gene cause defect IK_s potassium channels with a phenotype of LQT1. Boys with LQT1 have higher risk of ventricular arrhythmias and fatal events than girls. The trend switches in puberty to lower risk in males and higher risk in females.[43] Therefore, if there have been no events until the age of 16, risk of arrhythmias in males decreases, while in females it remains the same or increases.[43,44]

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The most prominent sex differences are found in LQT2. Mutations in the KCNH2 gene causing defect IKr potassium channels confer higher risk of arrhythmias in post-pubertal females compared with men and risk of cardiac events in LQT2 females remains increased both during childhood and adulthood.[43,45] Therefore, women with LQT2 and QTc >500 ms are considered high-risk individuals compared with men and should be evaluated for primary preventive implantable cardioverter-defibrillator (ICD) implantation.[42,46] Interestingly, in LQT2 women, risk of arrhythmias remains higher also after menopause, suggesting that lifelong Follow-up and continued long-term therapy[47] are needed. The reason for this finding is not fully known.

In LQT2 women, the risk of arrhythmias increases in the post-partum period, including the first 9–12 months after delivery.[48] Beta-blocker therapy should be continued during pregnancy and under no circumstances be reduced in the post-partum period.[48] Management of mothers with LQT2 should also consider that sleep deprivation is a risk factor for arrhythmic events which should be prevented.[49] A home automatic external defibrillator or a wearable defibrillator may be advocated in mothers as a bridge during the post-partum period when ICD is not indicated or accepted by the patient.

LQT3 is caused by mutations in the SCN5A gene encoding the sodium channel. LQT3 children seem to have lower risk of events compared with LQT2 and LQT1 children, but risk increases in adulthood.[43] 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.[50,51] There are conflicting reports on sex differences in ventricular arrhythmias in LQT3, both indicating higher risk in LQT3 men[52] or indicating no additional risk in LQT3 according to sex.[43] Beta-blocker efficacy may be greater in women with LQT3 compared with men.[53]

In animal studies using transgenic LQT2 rabbits, oestradiol exerted a pro-arrhythmic effect, while progesterone exerted an antiarrhythmic, protective effect.[54] In healthy volunteers with acquired LQTS, drug-induced QT prolongation is more pronounced and the risk for drug- induced arrhythmias is higher at the time of menstruation and during the follicular phase (when the oestradiol level is high) than during the luteal phase (when the progesterone levels is relatively high).[55] These observations suggest a pro-arrhythmic role for oestradiol and an antiarrhythmic effect of progesterone in humans[36] though this hypothesis has not been tested in women with congenital LQTS syndrome.

Key points

- An automatic external defibrillator or wearable defibrillator may be considered in high-risk women with QTc >500 ms post-partum when an ICD is not otherwise indicated or accepted by the patient.
- Women with LQTS have an increased risk during the 9 month post-partum period, in particular women with the LQT2 genotype.

Brugada syndrome

Brugada syndrome is genetically diagnosed in approximately 20–25% of clinical cases and has been linked to mutations in 10 different genes, of which the SCN5A gene encoding the sodium channel and Ito channels are the most important.[42] 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.[56,57] There is no full mechanistic understanding of sex differences, however, it has been suggested that androgens may affect the I_{to} channel and aggravate ion channel dysfunction.[58] Hormonal effects on the Brugada phenotype would also explain the regression of the typical ECG features in sterilized men.[59] The effects of oestrogens in Brugada syndrome are less well known. Pregnancy and the peripartum period seem to be well tolerated in women with Brugada syndrome.[60] Whether the risk of arrhythmias changes in post-menopausal women is unknown. Furthermore, ECG changes in Brugada syndrome women during the menstrual cycle, pregnancy, and menopause are not well known.

There are no systematic reports on sex differences in rare channelopathies such as short QT syndrome or in patients with CPVT. The unreported sex differences may be due to lack of studies and affected patients.

Key points

- Clinical manifestations of Brugada syndrome are eight-fold more frequent in adult men than in adult women.

Consensus recommendation	Supporting references
Beta-blocker therapy should be continued during pregnancy and post-partum in all LQTS women	42
Sex differences in LQTS should be considered in risk stratification for ventricular arrhythmias with generally higher risk of arrhythmic events in pre-pubertal boys and in women after puberty	42–44,49,52

Cardiomyopathies

Arrhythmogenic cardiomyopathy and HCM in their genetic forms are autosomal dominant and therefore inherited in equal measure by men and women. Penetrance, however, is generally higher in men.[42,61]

Arrhythmogenic right ventricular cardiomyopathy

In ARVC, cardiac penetrance is reported to be three-fold higher in men compared with women.[62] Men are also more frequently probands, are more severely affected and male sex has been reported as a risk factor for ventricular arrhythmia.[63] The reasons for the higher penetrance and arrhythmic risk in men are not clear, but recent reports have indicated that sex hormones influence cardiac outcome in ARVC.[64] It is known that athletic activity has a major impact on disease severity and progression[65,66] but sex differences in athletic activity in ARVC patients are not explored. Diagnosis of ARVC is complex including parameters from imaging, resting 12-lead ECG and

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Holter, genetic testing, family history, and tissue properties.[67] Imaging parameters for ARVC diagnosis are adjusted for body surface area,[68] but otherwise no sex-specific differences in diagnosing or management of ARVC patients are established.

Hypertrophic cardiomyopathy

In HCM, penetrance of disease is higher in men,[42,69] and a 3:2 ratio in male vs. female has been reported.[70] Therefore, women are more frequently non-penetrant mutation carriers compared with men. Importantly, risk of ventricular arrhythmias in women with HCM is at least equal to risk in men.[70] Therefore, in women with HCM, arrhythmic risk should not be underestimated. Women are also reported to be older at diagnosis, more frequently symptomatic and at higher risk for death from heart failure (HF) or stroke compared with men.[70]

Key points

- Sex differences are present in ARVC including higher disease penetrance of ARVC in men.
- Male sex has been reported as a risk factor for ventricular arrhythmias in some studies in ARVC patients, but results are inconsistent.
- Women with HCM have equal risk of ventricular arrhythmias as men. Sex should not be considered in risk stratification for ventricular arrhythmias in patients with overt HCM.
- Sex differences are present in HCM with higher disease penetrance in men.

Recommendation for studies

Future studies should address the following questions:

i. whether there are any sex differences in arrhythmic events in patients with CPVT;
ii. what the potential mechanisms for sex differences in disease penetrance and expression in ARVC are; and
iii. how pregnancy affects cardiac function in HCM.

Supraventricular ectopies and supraventricular tachycardia

Supraventricular ectopies

In the Cardiovascular Health study carried out in a population of healthy subjects >65 years of age in the early 90's the prevalence of frequent supraventricular ectopies defined as ≥15/h was significantly more often found in men (28, 2%) compared with women (18, 1%), $P < 0.0001$ and increased with age in both sexes.[71] In the Copenhagen heart study also of apparently healthy individuals age 55–75 years, an excessive number of supraventricular ectopies defined as ≥30/h or runs of >20 supraventricular ectopies was found in 35.4% women and 42.5% of men ($P = 0.183$).[72] These arrhythmias were associated with a 60% increase in the rate of death or stroke after adjustment for other risk factors. Furthermore, it was associated with a 2.7-fold increased rate of AF with >6 years follow-up. For each increase of 10 supraventricular ectopies per hour, the risk of the primary endpoint of death or stroke increased by 27% and the risk of AF by 50%. No sex adjusted results on these endpoints were available.

In conclusion, supraventricular extra-beat appear to be equally prevalent in both sexes. Although there is no clear definition of excessive supraventricular extra-beats these findings suggest that a cut-off of >30/h may constitute a risk. Actions to be taken could involve optimization of hypertension management with drugs that block the renin-angiotensin system which in turn may prevent the development of AF in both women and men.

It remains unclear if women experience more symptoms from atrial extra-beats than men, but it may be speculated that have worse quality of life since women with all types of paroxysmal arrhythmias have worse quality of life than men, with anxiety being the leading symptom.[30]

Paroxysmal supraventricular tachycardia

There is a clear sex-dependent difference in arrhythmia incidence and timing of the three most common types of paroxysmal supraventricular tachycardia (PSVT), i.e. AV nodal re-entrant tachycardia (AVNRT), accessory pathway mediated orthodromic AV re-entrant tachycardia (ORT), and less clear in focal atrial tachycardia (FAT).[30,73] Inappropriate sinus tachycardia (IST) was previously believed to occur predominantly in young, females from small studies.[74,75] However, in a later study of 607 patients, the prevalence of asymptomatic IST was 1.16%, in both sexes. Thus, IST might occur equally often in men than in women, but women seem to be much more symptomatic from IST.

Atrioventricular nodal re-entrant tachycardia and focal atrial tachycardia

The risk of developing AVNRT is almost twice as high in women than in men,[30,73] which probably is linked to sex differences in electrophysiological properties (*Figure 5*). Women have shorter slow pathway refractoriness with a wider vulnerability window whereas dual pathways are as common as in men.[76] There is conflicting evidence of the incidence of FAT in women compared with men some reporting a greater proportion of women and others no difference.

Accessory pathway and orthodromic re-entrant tachycardia

Orthodromic re-entrant tachycardia is twice as common in men as in women.[30,73,77] This correlates to the doubled incidence of accessory pathways in men as compared with women, and consequently, VF due to an antegradely conducting accessory pathway occurs less often in women than men.[78] The location of the accessory pathway in women is more often right-sided.[30]

Quality of life, time of diagnosis, and type of proposed therapy

The clinical challenge in the diagnosis of PSVT especially in AVNRT and FAT is to consider this diagnosis since there are no apparent signs in the ECG during sinus rhythm. In addition, ECG documentation during tachycardia is often difficult to obtain.[79,80] Therefore, these types of PSVTs are often misdiagnosed as panic attacks especially in women.[81] To increase detection rate an extended ambulatory ECG monitoring has been recommended.[82]

Quality of life is impaired in all PSVT patients, but women have worse quality of life and suffer more often from tachycardia related

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anxiety which in turn increases the risk of being misdiagnosed.[79,80,81] One study found that—when PSVT was unrecognized or undocumented—women were more likely than men to have symptoms ascribed to panic disorders (65% vs. 32%, respectively; $P < 0.04$). During a 20-month median follow-up, electrophysiologically guided therapy resolved symptoms in 86% of patients; only 4% continued to meet diagnostic and statistical manual of mental disorders-IV panic disorder criteria without evidence of PSVT recurrence.[81] In a very recent study, these observations were confirmed.[83] Moreover female patients seen by female physicians were more likely to be referred for ablation whereas men were more likely to be referred when seen by male physicians indicating a lack of gender bias by a doctor of the same sex.[83]

Women more often receive more drug therapy for PSVT than men, and are referred significantly later for catheter ablation.[81,83] There are no described sex-differences in the short- and long-term success rates of PSVT catheter ablation or in complication rates.[80,84,85]

Paroxysmal supraventricular tachycardia and the menstrual cycle

There is a clear dependence of AVNRT susceptibility on cyclic hormone level changes, with increased number of AVNRT and other PSVT episodes early in cycle, which has been suggested to be due to shorter APD.[30,73,86] One study found a linear relationship between the number of PSVT attacks and oestradiol and progesterone levels[86] (*Figure 6*). Another study found that in women with a history of perimenstrual clustering of PSVT scheduling of elective electrophysiological procedures at times of low oestrogen levels (premenstrual) may facilitate the probability of a successful procedure.[87] The practical implication of this is to carry out PSVT ablations during the first days of the menstrual cycle when such arrhythmias may be easier to induce. Moreover such scheduling avoids the performance of an electrophysiological study in a possibly fertile period or during early pregnancy. It is also of interest that attacks of AVNRT are more common in women in the perimenopause with declining oestrogen and that most women who undergo ablation for such arrhythmia are around 50 years of age or older.[83]

The overall conclusion is that low oestrogen levels (rather than high progesterone) are the reason for more supraventricular tachycardia in the early menstrual cycle and why AVNRT ablations are more common postmenopause.

Key points

- Women have a 2–3 times higher risk to develop AVNRT and than men.
- Orthodromic re-entrant tachycardia is twice as common in men as in women.
- Paroxysmal supraventricular tachycardia is more common in the luteal phase of the menstrual cycle.
- Paroxysmal supraventricular tachycardia affects quality-of-life more in women than in men.
- Women are referred for catheter ablation for PSVT later than men.
- Catheter ablation for PSVT is as successful and safe in women as in men.

Consensus recommendations	Supporting references
Women with symptoms suggestive of PSVT should undergo ambulatory ECG monitoring	77,82
In symptomatic women with documented PSVT, equal access to catheter ablation as appropriate should be provided	77
A diagnostic electrophysiological study may be offered to women with symptoms strongly suggesting PSVT, even before arrhythmia documentation	
In women with a previous 'negative' electrophysiology study, a second electrophysiology study timed in the first days of menstrual cycle may be advised to render arrhythmia inducible.	87

Knowledge gaps

What explains the sex differences in the prevalence of AVNRT, FAT, and ORT?

The relationship between psychological stress and PSVT; do women react differently to stress than men with regard to PSVT occurrence?

Are PSVT symptoms and the characteristics of documented PSVT different between women and men?

Recommendation for studies

To study, if the use of smartphone applications will shorten the time to detect symptomatic PSVT in women and men.

To investigate whether there is a critical atrial ectopic burden that initiates episodes of paroxysmal AF and whether the burden differs between sexes.

Atrial fibrillation comorbidities, symptoms, and therapy

The age-adjusted incidence and prevalence of AF are lower in women. Women with AF are older, have a higher prevalence of hypertension, valvular heart disease, and HF with a preserved ejection fraction (HFpEF) and a lower prevalence of coronary heart disease in comparison with men.[88] Although the presence of valvular disease in women has decreases, globally, the prevalence of valvular heart disease among individuals with AF is still greater than 25%, largely caused by the higher incidence of rheumatic heart disease in low-income and middle-income countries.[89] Despite experiencing more symptoms, women are less likely to receive rhythm control treatment than men. In ORBIT-AF, the use of antiarrhythmic drug (AAD) therapy was similar in men (28.6%) and women (28.9%).[90] However, women were

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less likely to undergo an electrical cardioversion (26.7% vs. 32.4%, $P < 0.001$) and to be referred for AF ablation (4.9% vs. 5.9%, $P = 0.04$). In contrast, women were more likely to undergo AV node ablation for rate control (2.9% vs. 1.7%, $P < 0.001$). Similar differences in treatment patterns for men and women were reported by two other recent registries.[91,92] The reason for these differences is unknown and warrants further investigation, although it may be associated with differences in age and associated conditions.[88]

In addition, women are more likely to experience serious adverse events by rhythm control. In the Rate Control vs. Electrical Cardioversion (RACE) trial, women with persistent AF had a higher incidence of the serious adverse effects of AAD, rate of pacemaker implantation and CV mortality, HF hospitalizations, and thrombo-embolic complications (*Table 2*).[93]

Key points

- Women with AF are older, have a higher prevalence of hypertension, valvular heart disease, and HFpEF and a lower prevalence of coronary heart disease compared with men.
- Women with AF have more severe symptoms than men.
- Women are equally likely to receive AAD as men.
- Women are less likely to undergo an electrical cardioversion receive cardioversion and PVI ablation than men.
- Women are more likely to undergo AV nodal ablation for AF than men.
- Women treated with rhythm control therapy have a significantly higher rate of life-threatening adverse events compared with men.
- Women seem more likely to develop sinus node disease during rhythm control management and to need a pacemaker for bradyarrhythmias.[94]

Thrombo-embolic risk and anticoagulation therapy for female patients

Atrial fibrillation currently affects at least 12.6 million females and 20.9 million males worldwide,[95,96] and growing global AF burden represents a major healthcare problem[97,98] owing to significant AF-associated morbidity including increased risk of stroke and death.[88,99,100] Females with AF are significantly older, with greater co-morbidity[92,101–105] (*Figure 7A*), and female sex is included in the CHA_2DS_2-VASc score (*Figure 8*) recommended by international AF management guidelines for thrombo-embolic risk assessment.[2,106]

Individual AF-related stroke risk is not homogeneous, and the strongest single risk factors for stroke are previous stroke and ageing.[107] Observational studies and randomized clinical trials (RCTs) consistently report higher crude stroke rates in females compared with male AF patients, but it is less clear whether female sex significantly contributes to individual stroke risk independently of other risk factors (*Table 3*). Previous systematic reviews of independent stroke risk factors in AF yielded conflicting results regarding female sex,[108,109] whilst a recent meta-analysis of 17 studies (including five RCTs) revealed an overall stroke risk ratio of 1.31 (1.18–1.46) for female sex,[110] with considerable heterogeneity among the studies regarding endpoint definition, treatment, and residual confounding factors.

A recent large observational AF study reported an unadjusted 19.0% (17.0–20.1%) population-attributable stroke risk for female sex, with a significant association that remained on extensive multivariable analysis.[111] Notably, this and other studies reported significant interactions between female sex and age or other stroke risk factors, with female sex being independently associated with stroke particularly at age ≥65[112,113]–75 years[111,114–116] *Figure 9*. In a recent population-based study with >10 000 follow-up events, female sex was non-significantly associated with stroke on extensive multivariable analysis accounting for time-varying exposures and covariates[117] (*Table 3*).

Usually, AF-related strokes are more severe than strokes from other causes,[118,119] with high 30-day mortality (24–33%) or severe permanent disability (35%).[120,121] In AF patients with acute stroke, female sex was associated with greater initial stroke severity[122] and worse long-term outcomes (i.e. dependency and stroke recurrence, but not mortality),[123] independent of age or other potential contributors. Among AF patients with prior stroke taking oral anticoagulant (OAC) therapy, female sex was associated with significantly lower

Table 2 Cardiovascular outcome in the RACE trial[93] in female vs. male patients

Endpoint, %	Female patients			Male patients		
	Rate control ($n = 95$)	Rhythm control ($n = 97$)	Absolute difference (90% CI)	Rate control ($n = 161$)	Rhythm control ($n = 169$)	Absolute difference (90% CI)
Endpoint	10.5	32.6	-21.4 (-32.3 to 10.5)	21.1	17.2	4.0 (-4.0 to 11.9)
Death from cardiovascular causes	3.2	10.3	-7.2 (-13.3 to -1.0)	9.3	4.7	4.6 (-0.2 to 9.4)
Heart failure	1.1	6.2	-5.1 (-9.6 to -0.6)	5.0	3.6	1.4 (-2.3 to 5.2)
Thrombo-embolic complications	2.1	11.3	-9.2 (-15.4 to -3.1)	7.5	5.9	1.5 (-3.2 to 6.2)
Bleeding	2.1	1.0	1.1 (-1.9 to 4.1)	6.2	4.7	1.5 (-2.8 to 5.7)
Severe adverse effects of AAD	–	9.3	-9.3 (-14.4 to -4.2)	1.2	1.8	-0.5 (-2.8 to 1.7)
Pacemaker implantation	2.1	5.2	-3.0 (-7.6 to 1.5)	0.6	1.8	-1.2 (-3.1 to 0.8)

Outcome represents the primary endpoint consisting of a composite of death from cardiovascular cause, heart failure, thrombo-embolic complications, bleeding, severe adverse effects of AAD, and the need for a pacemaker implantation. The composite and its components are presented in the table.
AAD, antiarrhythmic drug; CI, confidence interval.

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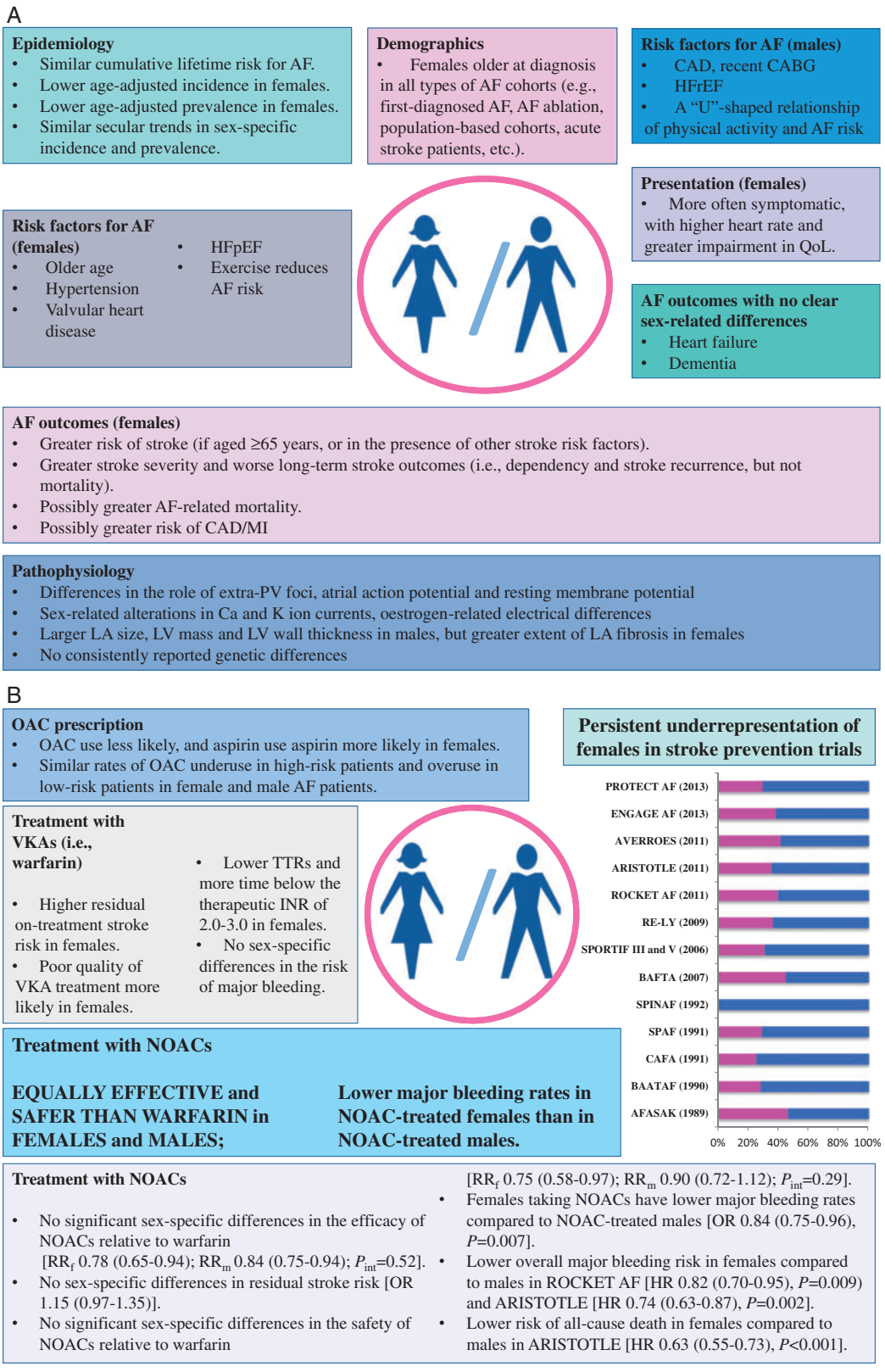

Figure 7 (*A*) Sex-specific differences in epidemiology, clinical presentation and major outcomes of patients with atrial fibrillation. (*B*) Sex-specific differences in anticoagulant therapy. AF, atrial fibrillation; CAD, coronary artery disease; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LA, left atrium; LV, left ventricle; MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; OR, odds ratio; PV, pulmonary vein; QoL, quality of life; RR, relative risk; VKA, vitamin K antagonist.

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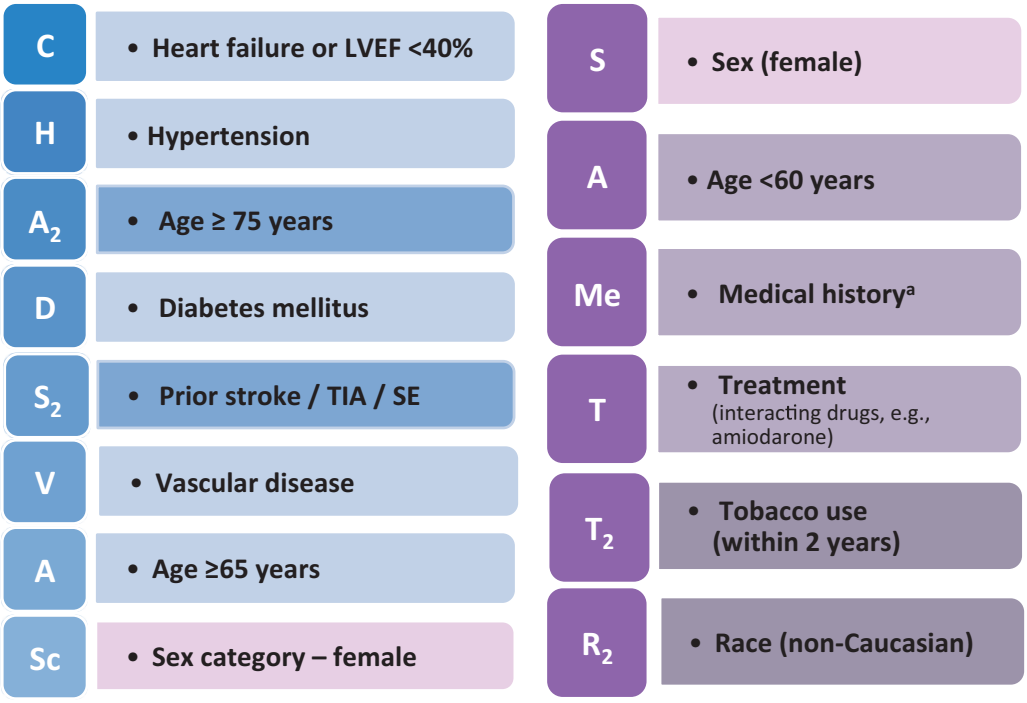

Figure 8 The CHA_2DS_2-VASc score for stroke risk assessment in patients with AF (left panel) and SAMe-TT_2R_2 score for the prediction of poor quality of VKA treatment in OAC-naïve patients. CHA_2DS_2-VASc: age ≥75 years and prior stroke/TIA/SE score two points each, whilst each of the other risk factors scores one point. SAMe-TT_2R_2: [a]Me scores one point in the presence of more than two of the following: hypertension, diabetes mellitus, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, and hepatic or renal disease; tobacco use and non-Caucasian race scores two points. LVEF, left ventricular ejection fraction; SE, systemic embolism; TIA, transient ischaemic attack.

risk of recurrent stroke [adjusted hazard ratio (HR) 0.70, 95% confidence interval (CI) 0.50–0.97].[124]

Compared with control, OAC using well-managed vitamin K antagonists (VKAs)[125] or non-vitamin K antagonist oral anticoagulants (NOACs)[126–130] effectively reduce AF-related thrombo-embolic events and all-cause mortality in their respective RCTs, but females were largely under-represented in all these RCTs (*Figure 7B*). Contemporary registry-based data show broadly similar OAC use in female and male AF patients,[90,92,101,131,132] but in several reports female AF patients at risk of stroke were less often prescribed OAC[133,134] and were given aspirin more often than their male counterparts.[134]

The available evidence showed no significant sex-specific differences in the VKA-related risk of major bleeding in AF patients,[135,136] although overall bleeding rates were higher in females owing to more minor bleeding.[137] However, warfarin-treated females had a 28–54% higher residual thrombo-embolic risk than males[135,138] (*Table 3*), even with well-managed warfarin [as measured by a time in therapeutic range (TTR) of ≥65–70%].[138] Good TTR is essential for effective stroke prevention with VKAs,[139,140] but female sex has been associated with lower TTRs[138,141] and more time below the therapeutic range compared with males.[138] Female sex weighs one point in the SAMe-TT_2R_2 score (*Figure 8*), which helps identifying new OAC users who would not do well on VKAs (i.e. those with SAMe-TT_2R_2 >2).[142,143]

Safety advantages of NOACs over warfarin were consistent in both sexes in a meta-analysis[144] of the RE-LY (dabigatran 150 mg or 110 mg b.i.d.),[126] ROCKET-AF (rivaroxaban 20 mg),[127] ARISTOTLE (apixaban 5 mg b.i.d.),[129] and ENGAGE AF-TIMI 48 (edoxaban 60 mg or 30 mg)[128] trial. Likewise, individual subgroup analyses showed no significant sex-specific differences in the major bleeding rates with apixaban or edoxaban (both doses) relative to warfarin, whilst rivaroxaban was associated with increased bleeding risk in males (HR 1.12, 95% CI 1.02–1.22) but not in females.[127] In the ROCKET-AF and ARISTOTLE trials, female sex was associated with overall lower bleeding risk compared with males,[145,146] (*Figure 7B*). Another meta-analysis including only NOAC arms from the ARISTOTLE. AVERROES, RE-LY (150 mg) and ROCKET-AF trials reported significantly lower NOAC-related bleeding risk in females compared with males [odds ratio (OR) 0.84, 95% CI 0.75–0.96].[135] In contrast to VKAs, the efficacy of NOACs relative to warfarin was consistent in both sexes,[144] with no sex-specific difference in residual stroke risk on NOACs[135] (*Table 3*).

Recent indirect comparison of NOACs effects using data from their respective landmark RCTs did not reveal any clinically relevant difference in NOACs efficacy and safety relative to female sex,[147]

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Table 3 **Female sex-related stroke risk in patients with atrial fibrillation**

Study	Cohort size (females)	Follow-up	Stroke number/ event rates	Adjusted risk[a] (95% CI)
Non-OAC observational cohort studies				
Framingham Heart Study[152]	705 new-onset AF (48%)	Mean 4.0 years	All *n* = 83	HR 1.92 (1.20–3.07)
ATRIA[114]	13 559 (43%)	15 494 person years	All *n* = 369	Overall RR 1.6 (1.3–1.9)
			F: 3.5%; M: 1.8%	Age ≤75 years: RR 1.6 (1.0–2.3)
				Age >75 years: RR 1.8 (1.4–2.3)
Danish Registry Study[153]	73 538 (51.2%)	1, 5, and 10 years	Hospitalization for. or death from stroke/SE	1 year: 1.6 (1.02–2.49)
				5 years: 1.25 (0.96–1.63)
				10 years: 1.24 (0.98–1.57)
The UK General Practice Study[154]	79 844 (50%)	Median 2.9 years	NR	HR 0.95 (0.84–1.06)
Swedish Cohort AF Study[155]	90 490 (47%)	Median 1.4 years	All *n* = 2519	Stroke: HR 1.21 (1.14–1.28)
				Stroke/TIA/SE: HR 1.17 (1.11–1.22)
Swedish Nationwide Cohort AF Study[111]	100 802 (50.3%)	Median 1.2 years	All *n* = 7221; 5.2% rate	Overall HR 1.18 (1.12–1.24)
			F: 6.2%; M: 4.2%	Age <65 years: HR 1.10 (0.86–1.41)
				Age 65–74 years: HR 1.11 (0.97–1.27)
				Age ≥75 years: HR 1.23 (1.17–1.30)
Danish Nationwide Cohort AF Study[115]	87 202 (51.3%)	1 year	Stroke/SE: all *n* = 5470	Age <65 years: HR 0.89 (0.70–1.13)
			F: 9.20%; M: 6.34%	Age 65–74 years: HR 0.91 (0.79–1.05)
				Age ≥75 years: HR 1.20 (1.12–1.28)
Quebec Population-based Cohort AF Study[117]	147 622 incident AF (51.8%)	Mean 2.9 years	All *n* = 11326; 2.6%	Time-fixed adjustment for confounders: HR 1.16 (1.11–1.21)
				Time-dependent adjustment for confounders: HR 1.01 (0.97–1.05)
Non-OAC arms of stroke prevention RCTs				
Atrial Fibrillation Investigators[156]	3432 (34%)	1802 person years	All *n* = 91 (81 ischaemic strokes)	Univariate analysis: HR 1.2 (0.8–1.8)
			F: 5.8%; M: NR	Multivariable analysis: NR
EAFT[157]	375 (47%)	Median 1.6 years	All *n* = 78	HR 1.5 (1.0–2.4)
SPAF[158]	2012 (28%)	Mean 2 years	All *n* = 130	HR 1.6, *P* = 0.01 (95% CI: NR)
			F: 4.4%; M: 2.1%	
BAFTA[159]	665 (45%)	Median 2.2 years	All *n* = 54	HR 0.99 (0.57–1.70)
Mixed OAC/non-OAC observational cohort studies				
Stollberger *et al.*[160]	403 (36%)	Mean 58 months	All *n* = 50	Univariate analysis: HR 1.3 (0.7–2.2)
				Multivariable analysis: reported as NS
Euro Heart Survey[161]	5333 (42%)	1 year	F: 2.2%; M: 1.3%	OR 1.83 (1.10–3.03)
Copenhagen City Heart Study[162]	276 (40%)	Mean 4.7 years	All *n* = 35	HR 2.6 (1.3–5.4)
			F: 5.17%; M: 1.98%	

Continued

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Table 3 *Continued*

Study	Cohort size (females)	Follow-up	Stroke number/ event rates	Adjusted risk[a] (95% CI)
Quebec Population-based Cohort AF Study[163]	83 513 recent-onset AF (52.8%)	NR	All *n* = 4266 F: 2.025%; M: 1.61%	Overall: HR 1.14 (1.07–1.22) At 1 year: HR 1.25 (1.23–1.38)
On OAC observational cohort studies				
Poli *et al.*[164]	780	Mean 3.1 years	All *n* = 40; 1.66%-rate F: 2.43%; M: 1.20%	OR 2.9 (1.5–5.6)
Poli *et al.*[165]	3015 (54.9%)	NR	Stroke/TIA: All *n* = 112	Univariate analysis: OR 1.2 (0.8–1.9) Multivariate analysis: NR
On OAC RCTs				
SPORTIF[137]	7329	Mean 1.5 years	Stroke/SE: all *n* = 184 F: 1.98%; M: 1.51%	Univariate analysis: HR 1.44 (1.07–1.93) Multivariable analysis: NS
Meta-analysis of the warfarin arms in the RE-LY, ROCKET AF, ARISTOTLE, BAFTA, and SPORTIF III and V trials[135]	26 260 (36.1%)	NA	All *n* = 827 F: 3.67%; M: 2.85%	OR 1.28 (1.11–1.47)
AFFIRM (*post hoc* analysis)[138]	4060 (39.3%; ≈90% on OAC)	NR	All *n* = 157 strokes F: 5.0%; M: 3%	HR 1.54 (1.10–2.16)
Meta-analysis of the NOAC arms in the RE-LY, ROCKET AF, ARISTOTLE, and AVERROES trials[135]	26 791 (39.0%)	NR	All *n* = 587	HR 1.15 (0.97–1.35)

AF, atrial fibrillation; AFFIRM, atrial fibrillation follow-up investigation of rhythm management; ARISTOTLE, apixaban for reduction in stroke and other thrombo-embolic events in atrial fibrillation; ATRIA, anticoagulation and risk factors in atrial fibrillation; AVVEROES, apixaban vs. acetylsalicylic acid to prevent stroke in atrial fibrillation; BAFTA, Birmingham atrial fibrillation treatment of the aged; CI, confidence interval; EAFT, European atrial fibrillation trial; F, female; HR, hazard ratio; M, male; NA, not applicable; NOAC, new oral anticoagulants; NR, not reported; NS, non-significant; NS, not significant; OAC, oral anticoagulant; OR, odds ratio; RCT, randomized controlled trial; RE-LY, randomized evaluation of long-term anticoagulation therapy; Rocket AF, Rivaroxaban Once Daily Oral Direct factor Xa Inhibition compared with Vitamin K Antagonist for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RR, relative risk; SE, systemic embolism; SPAF, stroke prevention in atrial fibrillation; SPORTIF, stroke prevention using oral thrombin inhibition in atrial fibrillation; TIA, transient ischaemic attack.
[a]Adjusted risk for stroke or stroke/SE, as defined in the respective study (see far left column).

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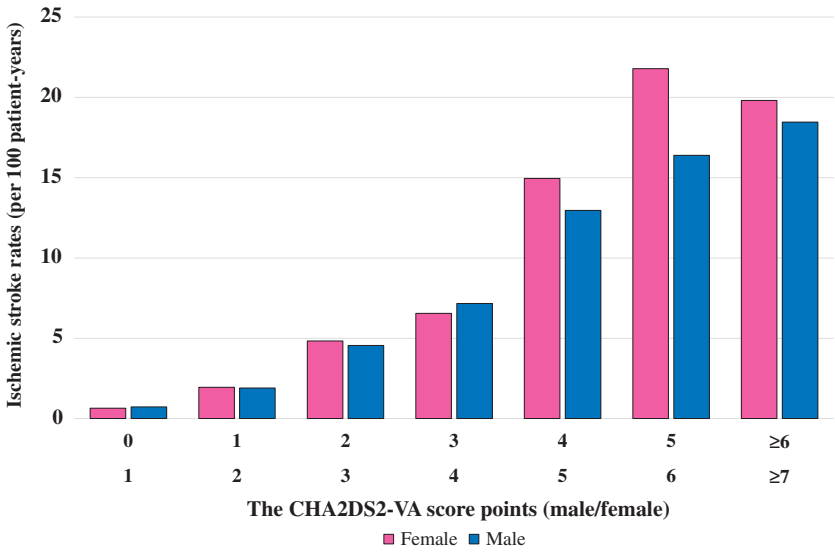

Figure 9 Ischaemic stroke rates in female and male AF patients according to the CHA_2DS_2-VASc score points. Reprinted with permission from Nielsen *et al.*[116] Absolute risk of thromboembolism among male (blue) and female (pink) are presented.

suggesting that the choice of particular NOAC in females should follow general principles of personalized AF treatment decision-making.[2,148]

Observational data addressing sex-related differences in NOACs effects suggest that both younger and older females are more likely to receive the lower dose of dabigatran (110 mg),[149,150] but male users of dabigatran 150 mg or 110 mg have less major bleeding (e.g. HR 0.73, 95% CI 0.59–0.90).[150,151] In elderly (>65 years) first-diagnosed AF patients, rivaroxaban 20 mg was associated with significant stroke reduction in males (HR 0.69, 95% CI 0.48–0.99) and more major bleeding in females (HR 1.20, 95% CI 1.03–1.42)[151] compared with Warfarin.

Key points

- Female sex is a stroke risk modifier that increases the risk of AF-related stroke in the presence of other conventional stroke risk factors.
- Female AF patients with acute stroke have a greater stroke severity and worse long-term outcome in terms of permanent disability, compared with males with AF.
- Anticoagulation with warfarin may be less well controlled in female AF patients compared with males, thus affecting the effectiveness of warfarin in female patient; moreover, females with AF have a greater residual stroke risk even with well-controlled VKAs.
- The efficacy and safety of NOACs relative to warfarin in the respective pivotal RCTs were consistent in both sexes, but females were largely under-represented in those trials.
- Given the lack of significant treatment interactions with sex, the choice of particular NOAC in females should follow general principles of personalized AF treatment decision-making.

Consensus recommendations	Supporting references
In AF patients, female sex is associated with an age-dependent moderate risk of stroke and should be regarded as a *stroke risk modifier* relevant in the presence of other CHA_2DS_2-VASc risk stroke factors, rather than an independent stroke risk factor	2,108,115
AF patients aged <65 years, with a CHA_2DS_2-VASc score of 1 due to female sex have low annual stroke rates (generally <1%) and do not need any antithrombotic therapy	2,106
Females with AF and ≥1 additional stroke risk factors (i.e. with a CHA_2DS_2-VASc score of ≥2) should be considered for OAC	2,106
NOACs are recommended in preference to VKAs females and males with AF	83,97
Aspirin should not be used for stroke prevention in females and males with AF, since aspirin is essentially ineffective and associated to similar risk of bleeding compared with NOACs or VKAs	2,106

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Knowledge gaps

More knowledge is needed on sex-specific differences in stroke and bleeding risk in patients with AF receiving contemporary therapies.

Sex-specific treatment patterns (e.g. greater likelihood of prescribing aspirin or lower dose dabigatran in female AF patients) need further investigation.

Recommendation for studies

Female patients must be adequately represented in the future AF trials.

Sex-specific barriers to the implementation of contemporary AF guidelines and the use of guideline-recommended OAC therapy need to be identified and addressed.

Catheter ablation of atrial fibrillation

Access to catheter ablation of atrial fibrillation

The main drivers for the invasive treatment of AF are symptoms and loss of quality-of-life due to the arrhythmia, as classified in the EHRA AF or other symptoms scores. Looking separately at quality of life in paroxysmal and persistent AF, palpitations and fear/anxiety occur mostly in paroxysmal AF.[101,166] Persistent AF patients suffer more from reduced exercise capacity and fatigue.[101,166,167] In a sub-analysis of the large Euro Observational research programme on AF (EORP-AF) including more than 3110 patients, women had significantly higher EHRA symptom scores than men. Palpitations and fear/anxiety were more prevalent in women, whereas other symptoms such as dyspnoea, chest pain, and fatigue were not different between sexes.[101]

It could thus be expected that women would undergo catheter ablation at least as often as men but in the German Ablation Registry[168] women represented 33% of the cohort ($n = 3652$), and presented significantly more often with paroxysmal AF than with persistent/long-standing persistent AF (72% vs. 28%). In men the distribution between both AF types was slightly more balanced (61% vs. 39%). Women referred for ablation were older than men, had less Coronary artery disease (CAD) but more valvular heart disease and hypertension. These findings are in line with two retrospective analyses from the USA and Canada.[169,170] In a large US retrospective study from 2000–12 of patients presenting to hospital for AF, female sex and Hispanic or black race were the strongest independent predictors for not getting catheter ablation therapy.[169] In a Canadian observational study investigating the 2003–12 period only 30% of ablated AF patients were women while they represented 42% patients presenting to hospital for AF.[170]

The same is true for RCTs of ablation for paroxysmal or persistent AF, where women are widely under-represented. In RCTs of ablation in paroxysmal AF, 29% of patients were women in the ADenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination (ADVICE) trial and 39% in the Fire and Ice trial.[171,172] For persistent AF, women representation in RCTs is even lower. In the most recent large RCT, the STAR AF II trial, out of 569 patients, only 19% were female.[173] Finally, in smaller or non-randomized observational studies (mostly to test new ablation approaches), women representation varied between 12% and 26% Thus, catheter ablation appears to be underused in women with paroxysmal but in particular for persistent AF.[174–176] The reasons for difference in treatment availability/supply and under-representation in RCTs are probably complex and may vary between countries. Amongst potential explanations may be a greater reluctance of women to receive invasive treatment and fear for complications by the referring cardiologists/treating physicians. Whatever reason, physicians, cardiologists, and electrophysiologists should be aware of this sex gap in the invasive treatment of AF and try to overcome it when appropriate.

Atrial fibrillation ablation outcomes and complications

There are three recurrent findings when analysing AF ablation procedures in women compared with men: (i) women are significantly older when presenting for AF ablation, (ii) women have a worse outcome regarding freedom from AF post-ablation, and (iii) some complications occur more frequently in women than in men.

Demographics and procedural data differences

Long-term follow-up in the Framingham study showed that at the index age of 40 years the lifetime risks for AF were 26.0% (95% CI 24.0–27.0%) for men and 23.0% (21.0–24.0%) for women.[177] In the same cohort women develop AF later in life than men.[178] In a more recent study of, 307 476 unique adult individuals who received a hospital diagnosis of AF; the mean age of men was 71.9 ± 12.3 years in men and, 82.2 ± 8.5 years in women strongly suggesting that women develop AF later in life than men.[179] Therefore, it may not be surprising that women undergoing AF ablation are on the average 4–6 years older than men at the time of ablation as evidenced from European, USA, and Canadian data.[168–170] There is a clear trend indicating that procedure times and radiofrequency (RF) energy application duration are shorter in women than in men, although the differences are not impressive (-10 to -19 min and -5 to -8 min vs. men, respectively).[168–170] The reasons for this difference is not entirely clear, but may be explained by the smaller left atrial size and a thinner left atrial wall in women, which might make transmural ablation lesions easier to achieve.

Outcomes of ablation for atrial fibrillation

While some smaller (long-term) observational studies found no difference in outcome between women and men[175,176] the majority of studies indicate female sex as a predictor for less favourable outcome in paroxysmal and persistent AF.[168–170,180,181] Female sex was also a major predictor of AF ablation procedural failure in most risk scores.[182]

The explanation could be related to the significantly older age of women or that women have more non-pulmonary vein (PV) mediated AF.[101,166] PVI might therefore be less effective than in men or younger patients in whom arrhythmogenic activity emanating from the PV may be the predominant AF mechanism. If this hypothesis was

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correct, the lower AF ablation success rates in women would reflect the failure of a specific ablation approach (PVI) in a substrate-mediated AF rather than indicating that women do 'by nature' worse when ablated for AF.

Complications of atrial fibrillation ablation

In most reports, complications related to AF ablation occur significantly more often in women than in men.[168,180–182] In several prediction models for AF ablation outcome, female sex is a negative 'risk' factor for procedure related complications.[183,184] Women tend to have more cardiac perforation/tamponade and groin complications (haematoma, vascular complications) than men which may be due to thinner left atrial wall in women, and older age at the time of ablation.[168,180–182]

In conclusion, AF ablation in women seems to be quicker to perform but women seem to respond less favourably to AF ablation and to have a significantly higher rate of procedural complications. It may be hypothesized that earlier AF ablation in women could improve outcome and decrease complications.

Key points

- Women with AF are referred for catheter ablation later than men, which may reflect that AF occurs later in life in women.
- Women presenting with AF suffer worse symptoms than men
- Women tend to have a less favourable result by PVI.
- Women suffer significantly more procedural complications from AF ablation including perforation/tamponade.

Consensus recommendations	Supporting references
Women suffering from symptomatic paroxysmal AF should be offered timely access to AF ablation when appropriate for medical reasons.	101,166
In symptomatic women with persistent or long standing persistent AF, rhythm control management including timely access to AF ablation should be offered ablation when appropriate for medical reasons.	101,166

Knowledge gaps

How does the substrate for paroxysmal and persistent AF differ with age and between women and men?

What is the location of the main substrate for paroxysmal and persistent AF in women?

Should AF ablation as a consequence be performed differently in women than in men?

How to create referral pathways across the health care system to ensure earlier referrals for AF ablation in particular in women?

Recommendation for studies

Female patients with AF must be adequately represented in the future AF ablation trials.

Testing of 'safer' catheter techniques to minimize risks of AF ablation in women.

To study if there is a sex difference in progression rates from paroxysmal to persistent AF.

Safety and efficacy of antiarrhythmic drug therapy

The acquired long QT syndrome

While the efficacy of Class I and III AAD therapy appears to be similar in men and women[185] the risk of severe adverse effects is not. (*Tables 2 and 4*).[93,185–190] Female sex has been associated with an increased risk of torsade de pointes and other drug associated adverse events. The mechanisms involved in the occurrence of torsades de pointes are described in Electrocardiography section. The acquired LQTS is clinically more common than congenital LQTS and is associated with female sex, electrolyte abnormalities, altered liver or renal function, HF, left ventricular hypertrophy, and the use of QT prolonging medication[191] (*Table 2*). Class IA and III AADs therefore have a higher risk of torsades de pointes in women than in men. To prevent torsades careful monitoring of the QT interval and potassium level, especially during initiation, as well as optimal therapy of HF, helps to reduce the risk of proarrhythmia. Avoidance of polypharmacy with other potassium antagonists and unmonitored drug formulation changes are important in the management of all patients taking Class IA and III agents, but they are particularly crucial in women with additional risk factors for torsades de pointes. Patient should be aware of symptoms associated with torsades. In case of symptoms of dizziness, or a new type of palpitations, an ECG and/or 24 h Holter monitoring is recommended because proarrhythmia with Class IA and III AADs occurs during bradycardia.

Key points

- Women have a greater risk to develop acquired LQT syndrome than men with Class IA and III AADs such as sotalol, dofetilide, ibutilide, and quinidine.

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Table 4 Sex differences in torsades de pointes occurrence in patients treated with Class I or III AAD

Study	AAD	Type of arrhythmia	Torsades de pointes (%) female vs. male	Other risk factors
Makkar *et al.*[186]	Class IA and III (MEDLINE Search)	Atrial and ventricular arrhythmias	Females 70% of 322 reported cases of torsades de pointes in a Medline search	NA
Lehmann *et al.*[187]	D, L- Sotalol	Atrial and ventricular arrhythmias	4.1% vs. 1.9%	History of HF Sotalol dose ≥320 mg/day
Torp-Pedersen *et al.*[188]	Dofetilide (DIAMOND HF study)	Prevention of AF was primary endpoint	NA	Female sex (OR 3.2) NYHA III/IV (OR 3.9)
Gowda *et al.* 2004[189]	Ibutilide	Atrial arrhythmias	5.6% vs. 3%	
Pedersen *et al.*[190]	Dofetilide	Post-MI and HFrEF population (DIAMOND studies)	47% vs. 28%	Female sex (OR 2.2) Recent MI (OR 0.3) NYHA III/IV (OR 3.9) QTc (OR 1.1)
Higgins *et al.*[185]	Quinidine		4.8% vs. 0%	

AAD, antiarrhythmic drug; AF, atrial fibrillation; DIAMOND HF, Danish Investigations of Arrhythmia Mortality on Dofetilide in Heart Failure; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; NA, not applicable; OR, odds ratio.

Consensus recommendation	Supporting references
Women treated with Class IA or III AADs should be aware of the risk and symptoms associated with torsades de pointes	2
Women treated with AADs should therefore, be periodically evaluated to confirm their eligibility for AAD treatment	2
Women with HF or pathological left ventricular hypertrophy should be offered amiodarone. Other AAD should be avoided	2
AF clinicians must offer effective diagnostic tools and therapeutic management to women and men equally to prevent stroke and death	2
In women ECG monitoring during initiation of AAD should be considered to monitor heart rate and QT prolongation and 1–2 weeks after dosage increase	
In women with long-term AAD ECG should be monitored every year to monitor heart rate and QT prolongation	
Class IA or III AAD should not be instituted in women with a prolonged QT interval (>500 ms), or those with a significant sinoatrial node disease or AV node disease without a functioning permanent pacemaker	

Knowledge gaps

Understanding the underlying biology for sex-specific differences in adverse events in AAD therapy.

Recommendation for studies

A priori specified secondary analyses of efficacy and complications of antiarrhythmic therapies by sex should be included in AAD RCTs.

Sudden cardiac death

Demographics

The lifetime risk of sudden cardiac death (SCD) in women is significantly less than in men across all index ages.[192] Long-term follow-up in the Framingham Heart study showed that at the index age of 45 years the remaining lifetime risk of SCD is 10.9% for men and 2.8% for women ($P < 0.001$).[192]

Epidemiological studies of SCD and sudden cardiac arrest (SCA) survivors suggest that the predominant mechanism behind the SCD event is a ventricular arrhythmia in the setting of underlying CAD.[192] Women have a lower incidence of SCD than men, even when accounting for predisposing risk factors such as CAD, myocardial infarction (MI), and HF.[192] The profile of women suffering from SCD may also differ from men both in underlying cause, clinical presentation and outcome. In the USA, more than one-third of SCD cases or approximately 150 000 events annually occur in women.[193] National incidences of SCD were estimated for women and men in the Oregon Sudden Unexpected Death Study (SUDS[193]). SCD rates among women were 45 per 100 000 (95% CI 37–53 per 100 000) and among men were 76 per 100 000 (95% CI 66–87 per 100 000). In a patient-level analysis of five clinical trials and registries that enrolled patients with HF, who met ACC/AHA/HRS guideline indications for, but did not receive an ICD or cardiac resynchronization therapy (CRT), sex-specific differences in predicted annual mortality were determined.[194] This analysis used the Seattle Heart Failure Model

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(SHFM) which predicts annual mortality using common clinical variables. Eight thousand, three-hundred and thirty-seven patients were analysed of whom 20% were women. Considering mode of death, the risk of SCD was 32% lower in women compared with men (HR 0.68; 95% CI 0.58–0.68; $P < 0.0001$), but no difference by sex was seen in HF deaths. Overall, these findings are largely in keeping with studies from Western Europe and Australia with similar populations albeit varying methodology.[195–197]

Coronary artery disease is the most common pathology underlying SCD. In white men, it is responsible for 70–75% of all SCDs[198,199] and found in 80–90% of men in cardiac arrest survivor studies and autopsy series. In women, the corresponding figure is 40–45% in the same studies. Coronary artery disease confers a 3.3-fold increase in long-term risk of SCD in men and only a 1.9-fold increase in long-term risk in women. HF confers a 4.8-fold increase in risk of SCD in men and only a 1.5-fold increase in risk in women.[200] In the Framingham Study, women have a four-fold higher risk of SCD following an MI as compared with men who have a 10-fold increased risk.[192] A retrospective study of a cohort of SCD survivors demonstrated that women were more likely than men to have a structurally normal heart.[201] Clinically, women who suffer from an out of hospital cardiac arrest are older, typically presenting with a 10 to 20 year delay in sudden cardiac event rates. Women are more likely to present with a non-shockable rhythm and/or experience their arrest at home as compared with men.[202] A large proportion of SCD occur among individuals without known heart disease. Sudden cardiac death may therefore be the first manifestation of their disease. This is true for approximately 44–52% of men and 59–69% of women who suffer SCD without previously diagnosed CV disease.[203]

Potential mechanisms for sex-related differences in sudden cardiac death and ventricular arrhythmias

In patients with CAD, the most common mechanisms precipitating SCD are thought to be polymorphic ventricular tachycardia (VT)/VF due to ischaemia and/or infarction and monomorphic VT degenerating into VF arising from a re-entrant circuit associated with myocardial scar.[204] As observed in several studies of patients with ICDs,[205,206] men and women have similar survival rates but men experience more appropriate therapy for VT/VF as compared with women. This may be due in part to a difference in underlying substrate with men generally presenting with more extensive CAD and scar formation. However, a lower rate of ventricular arrhythmias is seen also in women with CAD suggesting a difference in susceptibility to triggers of ventricular arrhythmias between men and women.[207] Proposed contributing factors include hormonal effects, such as the role of oestrogen in modulating norepinephrine release, thus influencing electrophysiological properties and/or autonomic function. In the Heart and Estrogen/Progestin Replacement Study (HERS) postmenopausal women with CAD who engaged in regular physical activity had a decreased risk of SCD, supporting the benefit of the modulating autonomic nervous system and increasing vagal tone.[208]

Survival after sudden cardiac arrest in women

Given the above findings it is perhaps not surprising that there are sex-related differences in outcome after an SCA event. A Danish nationwide registry study of 19 371 patients[209] from 2001–10 demonstrated an overall increase of survival. Thirty days crude survival increased in males (3% in 2001–12.9% in 2010) and in females (4.8% in 2001–6.7% in 2010) ($P < 0.001$). In an adjusted model, females were positively associated with survival in patients with a shockable rhythm. A recent meta-analysis[203] involving 13 studies and 409 323 patients support these findings. Women in the meta-analysis were more likely to present with SCA at home, less likely to have witnessed SCA, less likely to have an initial shockable rhythm but more likely to receive bystander cardiopulmonary resuscitation. After adjustment for these differences, women were more likely to survive at hospital discharge (OR 1.1, 95% CI 1.03–1.20; $P = 0.006$).

Key points

- Women have a lower incidence of SCD than men, even when accounting for predisposing risk factors such as CAD, MI, and HF.
- Women are less likely to have underlying CAD as a risk factor for SCD and more likely than men to have a structurally normal heart, suggesting a sex difference in arrhythmic substrate.
- Observational studies and registry data suggest improved survival after SCA in women.

Knowledge gaps

What is the epidemiology of SCD outside the US and Western Europe?

Better understanding of arrhythmic substrate and difference in susceptibility to triggers of ventricular arrhythmias between men and women is needed.

Why do women have a lower incidence of SCD than men, even when accounting for similar predisposing risk factors?

What is the role of hormonal effects on electrophysiological properties and autonomic function in women?

What are the sex-related differences in outcome after an SCA event?

Recommendation for studies

There is the need for large population- based studies that would include women to address the knowledge gaps in mechanisms of SCD and define sex-specific risk factors.

Ventricular tachyarrhythmia and catheter ablation

Idiopathic ventricular arrhythmias

Sustained ventricular arrhythmias are most often related to myocardial structural heart disease such as healed MI or cardiomyopathies. However, no apparent structural abnormalities are identified in approximately 10% of all patients referred for evaluation of VT.[210] Idiopathic ventricular arrhythmias usually have a benign course and SCD is rare. When the arrhythmia occurs as frequent premature ventricular complexes (PVCs) and/or non-sustained VT (NSVT) it can cause depressed ventricular function as a form of tachycardia-induced cardiomyopathy. In the absence of LV dysfunction, the therapy of idiopathic VT is largely guided by symptoms.

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Idiopathic ventricular arrhythmias are divided into subtypes according to the site of origin as right or left ventricular outflow tract (RVOT or LVOT), left ventricular intrafascicular (verapamil-sensitive) and perimitral or peritricuspid ventricular arrhythmias.[210] An early literature review of 748 patients with idiopathic VT included 387 (52%) female patients. RVOT-VT occurred twice more frequently in females, whereas verapamil-sensitive intrafascicular LV-VT was three times more frequent in males.[211]

In a small report of 47 patients with RVOT-VT sex-specific triggers were described. Twenty of 34 (59%) female patients reported RVOT-VT initiation with recognized states of hormonal flux (premenstrual, gestational, perimenopausal, and coincident with the administration of birth control pills).[212] In a more recent single centre study of 625 consecutive patients undergoing catheter ablation of idiopathic PVC/NSVT and VT 310 (50%) females were included.[213] The large majority (78%) of arrhythmias originated in the outflow tracts, 13% of arrhythmias were from the septal, peritricuspid or perimitral free wall region and 4% from the LV fascicles. RVOT arrhythmias were 1.5 times more frequent in women than in man, while LVOT and mitral annular arrhythmias were slightly and fascicular arrhythmias significantly more (4.4 male/female ratio) frequent in men. Left ventricular outflow tract arrhythmias increased with age.

Catheter ablation of idiopathic ventricular arrhythmias

Catheter ablation is a relatively effective option for monomorphic arrhythmias when causing severe symptoms, especially if medications are not effective, not tolerated or not desired.[210] Concerning outflow tract ablation the success rate varied between 58 and 100% and was dependent on the region of origin and was not different between females and males.[213] Similar results were reported in another recent large single centre study of 114 consecutive patients including 55 (48%) females without structural heart disease undergoing catheter ablation for monomorphic VT.[214] The baseline characteristics (ablation as first line therapy, failed amiodarone therapy), procedural data (RF time per procedure, epicardial ablation), ablation success, and complications rate were not different between males and females.

Key points

- RVOT-VT is twice more common in females.
- Female and male patients are equally represented in non-randomized single centre registries of catheter ablation for idiopathic ventricular arrhythmias.
- Catheter ablation of idiopathic ventricular arrhythmias is equally effective with the same risk of complications in female and male patients.

Ventricular arrhythmias associated with structural heart disease

The most common cause of scar-related VT is a prior MI.

Catheter ablation of ventricular arrhythmias associated with structural heart disease

Two large multicentre registries[215,216] and three randomized controlled trials[217–219] have investigated the role of catheter ablation in the treatment of VT following MI (*Table 5*). Female patients were severely under-represented in these trials constituting 6–13% of the study population. In other scar-related VTs as non-ischaemic cardiomyopathy (NIDCM) similar under-representation of female patients were reported in single centre registries. In the HELP-VT study, 17% of the 63 patients[220] and in a similar large single centre US study 22% of the 301 patients[214] undergoing catheter ablation for VT in the setting of NIDCM were females. Arrhythmogenic cardiomyopathy associated VT ablation registries reported variable but in general higher female participation. In a multicentre registry 42 (48%) of the 87 patients[221] and in two large single centre registries 17% (8 of the 46)[214] and 27% (17 of the 62)[222] of the patients with ARVC undergoing catheter ablation for VT were female.

In an early study female survivors of SCA (39 of 150 patients) were less likely to have inducible sustained VT (26% vs. 65%, $P < 0.001$) or any ventricular arrhythmia (38% vs. 87% in men, $P < 0.001$) during electrophysiological study.[223] In the MUSST study, the rate of inducibility was significantly higher in patients with a history of MI and in men compared with women.[224] A recent meta-analysis including five major trials data showed that women are less likely to receive appropriate ICD therapies (HR 0.63).[205] The reasons for lower susceptibility of women with structural heart disease to ventricular arrhythmias are unknown. Sex-dependent differences in the arrhythmogenic characteristics of the substrate may be an explanation. In a recent study in patients with ARVC men had larger endocardial and epicardial area with late potentials.[225] The above epidemiological data may partly explain why women are under-represented in both registries and randomized controlled trials of patients with structural heart disease undergoing catheter ablation of ventricular arrhythmias. Referral bias is likely another important factor similar to catheter ablation of AF and defibrillator therapy.

Outcome of catheter ablation

Recently, the International Ventricular Tachycardia Ablation Centre Collaborative Group compared the outcomes between women and men with structural heart disease undergoing ablation.[226] In this large registry of 12 high-volume ablation centres 2062 consecutive patients with structural heart disease undergoing catheter ablation were studied. The 13% (266 patients) of the study population were women [82 (31%) with ischaemic and 184 (69%) with NIDCM]. Women were more likely to have NIDCM than men (69% vs. 44%, $P < 0.001$). Compared with men, women were younger, less likely to have an ICD, with higher left ventricular ejection fraction (LVEF) and less VT storm, arguing against later referral with more advanced disease. Despite this, women had higher rates of VT recurrence at 1 year follow-up after ablation (30.5 vs. 25.3%, $P = 0.03$). Women and men with NIDCM had similar rates of VT recurrence (29.9% vs. 28.6%, $P = 0.55$). However, women with ischaemic cardiomyopathy were more likely to have recurrence than men with ischaemic cardiomyopathy (31.7% vs. 22.8%, $P = 0.02$). While the number of induced VTs, epicardial mapping and the use of haemodynamic support was similar, compared with men, women had shorter mean ablation time (33.2 vs. 40.6 min, $P = 0.004$). Complication rate in women were similar as in men (8.6% vs. 6.5%, $P = 0.22$). Differences in referral pattern, arrhythmia substrate or undertreatment were proposed as possible explanation for higher VT recurrence rate in women.

However, in another recent large single centre registry of 948 consecutive patients undergoing catheter ablation for sustained monomorphic VT, 174 (18%) were females with CAD (25%), NIDCM (37%), ARVC (5%), or without (33%) structural heart disease.[214]

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Table 5 Multicenter registries and randomized controlled trials of catheter ablation of ventricular tachycardia post-myocardial infarction

Study	Enrollment population	Therapy	Total enrollment (*n*)	Women, *n* (%)	Primary outcome	Sex-specific differences in primary outcome
Multicenter registries						
Multicenter Thermocool VT ablation Trial, 2008	Recurrent monomorphic VT post-MI	3DEAM guided irrigated tip VT ablation	231	25 (11)	53% freedom from recurrent VT after 6 months of follow-up	Success group: females 12% vs. failure group: females 9%, $P = 0.47$ 1 year survival group: females 8% vs. 1 year death group: females: 22%, $P = 0.009$
Post-Approval Thermocool VT Trial, 2016	Monomorphic VT post-MI	3DEAM guided irrigated tip VT ablation	249	15 (6)	62% freedom from recurrent VT after 6 months of follow-up	NR
Randomized controlled trials						
SMASH-VT Study, 2007	Post-MI patients undergoing ICD implantation for VT/VF	VT ablation and ICD vs. ICD	128	17 (13)	appropriate ICD therapy 33% in the ICD vs. 12% in the ablation + ICD group after 23 months of follow-up, $P = 0.007$	HR male: 0.37 (0.16–0.86), HR female: 0.00; $P = 0.99$
VTACH study, 2010	First episode of stable VT post-MI EF ≤50%	VT ablation and ICD vs. ICD	110	7 (6)	Time to first VT/VF recurrence 19.5 m in ablation + ICD vs. 5.9 months in ICD group, $P = 0.01$	NR
VANISH study	Post-MI monomorphic VT under AAD in ICD patients	VT ablation vs. Escalated AAD therapy	259	18 (7)	Death/VT storm/appropriate ICD shock 59% in ablation vs. 69% in escalated AAD group after 28 months of follow-up, $P = 0.04$	HR male: 0.74 (0.54–1.01), HR female: 0.59 (0.16–2.13); $P = 0.66$

3DEAM, three dimensional electroanatomical mapping; AAD, antiarrhythmic drug; EF, ejection fraction; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; MI, myocardial infraction; NR, not reported; SMASH-VT, substrate mapping and ablation in sinus rhythm to halt ventricular tachycardia; VANISH, ventricular tachycardia ablation vs. escalated antiarrhythmic drug therapy in ischaemic heart disease; VT, ventricular tachycardia; VTACH, ventricular tachycardia ablation in coronary heart disease.

Women undergoing first VT ablation were younger than men in patients with CAD (63 vs. 68 years, $P = 0.05$) and NICM (53 vs. 59 years, $P = 0.026$) but not with ARVC (46 vs. 48 years, $P = 0.85$). There was no other difference in baseline characteristics (ejection fraction, prior heart surgery, ablation as first line therapy, VT storm, and failed amiodarone use) between women and men. The ablation time was shorter in women than in men with NIDCM (15.7 min vs. 22.4 min, $P = 0.017$) but it was not different between women and men with CAD, ARVC, and absence of structural heart disease. Complications rates were the same in women as compared with man (7.1% vs. 6%, $P = 0.53$). There were no statistical differences in VT recurrence rates and mortality between women and men in any of the groups after a median follow-up of 270 days.

Key points

- Female patients are under-represented in randomized controlled clinical trials and registries of patients undergoing catheter ablation for VT with structural heart disease, especially with CAD.
- Lower incidence of SCD and CAD and lower incidence and inducibility of ventricular arrhythmias in women with structural heart disease partly explain the under-representation.

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- Catheter ablation of VT associated with ischaemic heart disease may be associated with slightly higher VT recurrence rate and has the same risk of complication in female and male patients.
- Catheter ablation of VT associated with NIDCM and ARVC is equally effective with the same risk of complications in female and male patients.

Consensus recommendations		Supporting references
Catheter ablation should be offered equally to women and men with symptomatic ventricular arrhythmias		210,213,214,226
Catheter ablation should not be denied to women with symptomatic ventricular arrhythmias because of feared less success or increased complication rates		213,226

Knowledge gaps

It is currently unknown why women have more frequently RVOT but not LVOT PVC/VTs and why intrafascicular re-entry occurs more frequently in men than women. The reasons for lower susceptibility of women with structural heart disease to ventricular arrhythmias are also unknown. The role of sex-dependent differences in the autonomic nervous system and/or in the arrhythmogenic characteristics of the substrate should be further studied. Referral bias for catheter ablation of ventricular arrhythmias and inclusion bias of female patients in randomized trials have not been studied in detail. It is unknown if female patients with smaller hearts should receive less RF energy to avoid complications or on the contrary, undertreatment of female patients during catheter ablation of scar-related ventricular arrhythmias leads to incomplete substrate modification and higher VT recurrence rates.

Recommendation for studies

Sufficient number of (or only) female patients should be included in RCTs of catheter ablation of ventricular arrhythmias associated with structural (especially coronary artery) disease to ensure adequate statistical power for analysis

Comparing sex ratio in screening and inclusion of all eligible patients should highlight if inclusion or referral bias is present.

Sex differences in target sites and effective ablation characteristics; in the case of scar-related arrhythmias in substrate characteristics should be investigated in single and multicentre registries. In case of VT recurrence, recurrence of the same clinical VT vs. appearance of new VTs may be investigated to identify undertreatment during the initial procedure.

Device-based therapies

Brady-arrhythmia therapy

There are limited contemporary data on sex differences in patients receiving pacemakers for the treatment of symptomatic bradycardia. Data from registries and randomized controlled trials of pacing modes indicate that women are older at the time of pacemaker implantation.[227,228] Women are more likely to have sinus node disease[229] and AF as the primary cause of bradyarrhythmias, whereas heart block is more often the primary indication for pacing in men.[230,231]

Rates of pacemaker implants in women

More men than women receive permanent pacemakers under the age of 80 years, whereas the ratio is reversed in those ≥80 years.[227] Other studies have confirmed the older age of women at the time of initial pacemaker implantation compared with men.[232] The overall proportion of men vs. women who receive permanent pacemakers has been the same in some studies,[233] while others have shown a male predominance.[234] The older age of development of bradycardia and the cause of bradycardia in women likely reflects the protective effect of sex hormones and delays in developing significant CV disease in women.

Some but not all reports suggest that women, particularly those greater than 80 years of age, are more likely to receive a ventricular pacing system compared with a dual-chamber pacing system. Other studies have shown that age affects choice of pacing system more than sex.[235] Whether some of these differences may be explained by associated comorbidities or persistent AF in women is uncertain. At the time of pacemaker implantation, women have been found to have slightly higher atrial pacing thresholds and smaller P-wave amplitudes compared with men, although the differences are small and probably not clinically relevant.[227]

Clinical outcomes

Unlike trials of implantable cardioverter-defibrillator therapy, women have been well represented in randomized trials of pacing mode (*Table 6*).[230,236–238] The proportion of women in these trials has ranged from 41 to 64%. Women compared with men experienced similar event rates of the major outcomes reported in these trials, including all-cause mortality. Other studies have found that women live longer than men after pacemaker implantation, even though their mean age at implantation is higher.[228,239] In a large registry trial outcomes (mortality) was similar between sexes for single and dual chamber pacemakers.[231]

Quality of life has been reported to improve in patients following pacemaker implantation for symptomatic bradycardia. Significant sex differences were not reported in the Canadian Trial of Physiologic Pacing (CTOPP).[240] In the MOde Selection Trial (MOST) in sinus node dysfunction, men reported higher quality of life scores and improved functional status compared with women.[241]

Complications

Some studies have shown a higher rate of complications such as pneumothorax, pocket hematomas, and lead perforation in women at the time of permanent pacemaker implantation.[227,242] Other studies have not shown a sex difference in complication rate,[243] although MOST showed a trend in that direction (6.0% complication rate in women vs. 3.8% in men, $P = 0.07$).[244] Any higher risk of complications in women may be related at least partially to their smaller body size. In the Danish pacemaker registry, women were reported to have a

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Table 6 Sex and cardiovascular outcomes in randomized clinical trials of pacing mode

Study	Design	Females, *n* (%)	Age (years)	Outcomes HR (95% CI)
CTOPP[236]	Ventricular vs. physiological pacing in patients with symptomatic bradycardia	1057 (41)	73 ± 10	Stroke or CV death[a] F: 0.83 (0.61–1.16) M: 0.96 (0.74–1.23)
MOST[238]	DDDR vs. VVIR in patients with symptomatic bradycardia secondary to SND	955 (47.5)	74 (IQR 67–80)	Death, stroke, or HF hospitalization F: 0.89 (0.71–1.13) M: 0.91 (0.73–1.15)
UKPACE[230]	VVI vs. VVIR vs. DDD pacing in patients with symptomatic bradycardia secondary to AV block	870 (43.0)	80 ± 6	All-cause mortality F: 1.02 (0.81–1.29) M: 0.95 (0.80–1.14)
DANPACE[235]	AAIR vs. DDDR in patients with symptomatic bradycardia secondary to SND	913 (64.5)	73 ± 11	All-cause mortality F: 1.08 (0.86–1.37) M: 0.98 (0.69–1.40)

Estimated from *Figure 3* Connolly *et al.*[236]
AAIR, atrial rate adaptive pacing; CI, confidence interval; CTOPP, Canadian Trial of Physiologic Pacing; DANPACE, Danish Multicenter Randomized Trial in Single Lead Atrial Pacing vs. Dual Chamber Pacing in Sick Sinus Syndrome; DDDR, dual chamber rate adaptive pacing; F, female; HF, heart failure; HR, hazard ratio; IQR, interquartile range; M, male; MOST, Mode Selection Trial; SND, sinus node dysfunction; UKPACE, United Kingdom Pacing and Cardiovascular Events; VVI, ventricular pacing; VVIR, ventricular rate adaptive pacing.

greater risk for complications than men, especially at lower body mass index (BMI) and in centres with small implantation volumes per physician.[242]

Key points

- Women are more likely to have sinus node disease and AF as the primary cause of bradyarrhythmias, whereas high degree AV block is more often the primary indication for pacing in men.
- Compared with men, women experience similar improvement in quality of life and similar rates of major adverse outcomes reported in pacemaker clinical trials, including all-cause mortality.
- Some studies have shown a higher rate of complications in women at the time of permanent pacemaker implantation, but this has not been a consistent finding.

Recommendation for studies

To study efficacy and complications of lead-less pacing in women.

Implantable cardioverter-defibrillators

Randomized clinical trials of implantable cardioverter-defibrillators in women

Left ventricular systolic dysfunction and severity of HF symptoms [New York Heart Association (NYHA) class) are currently the strongest predictors of SCD in patients with established CAD. Primary preventive ICD therapy is recommended as a Class I indication for patients with an LVEF of ≤35%, NYHA Class II–III at least 40 days post-MI or with NICM. Implantable cardioverter-defibrillator therapy is also indicated in patients who are survivors of a cardiac arrest due to VF or haemodynamically unstable sustained VT for secondary prevention purposes. While our current guidelines clearly apply to both men and women it is important to recognize the under-representation of women in clinical trials of ICD therapy as well as the underuse of this therapy in women, despite documented survival benefit.

Women have been under-represented in all RCTs of ICD therapy and represented 10–32% of patients enrolled in ICD trials (AVID, CIDS, CASH, MADIT II, DEFINITE, SCD-HeFT, MUSTT, DANISH, DINAMIT, and IRIS).[245–254] None of these trials were powered to determine a sex-specific outcome, though many reported the interaction by sex in the subgroup analyses. These are summarized in *Table 7*. Secondary sub-studies evaluating the benefit of ICD therapy in women were conducted in a few of these trials. In AVID[245], ICD therapy was associated with improved survival regardless of sex (women represented 20% of enrolees). Women were younger, had more NICM and VF rather than VT as the index arrhythmia.[255]

The results of MADIT II[248] and SCD-HeFT[250] trials both demonstrated a reduction in all-cause mortality in patients with moderate HF who received an ICD compared with standard medical therapy. MADIT II enrolled 1232 patients with CAD, LVEF <30%, and prior MI of whom 15% were women. No difference by sex was observed (HR for women vs. men, 0.57 vs. 0.66). The SCD-HeFT study enrolled 2521 patients with LVEF <35% to receive an ICD, or double-blinded amiodarone or placebo drug. Women represented 23% of the 2521 patients enrolled. Women were more likely to have a NIDCM compared with men (66% vs. 43%, respectively) and were more likely to have NYHA Class III HF compared with men (36% vs. 26%, respectively). No significant difference in ICD benefit by sex was observed, although the benefit for women was lower than in men [female: HR 0.96 (95th 0.58, 1.61) vs. male: 0.73 (0.57, 0.93)].[255] Several other sub-studies of the randomized ICD trials similarly found no statistical difference in ICD benefit by sex.[256–259]

Recently, 1116 (27.5% women) patients in a trial of ICD therapy compared OMT in patients with NIDCM. Fifty-eight percent of

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Table 7 Women in implantable cardiac defibrillator randomized clinical trials

Study	Enrollment population	Randomized therapy	Total enrollment	Women (%)	Primary outcome endpoint	Primary outcome in all patients	Interaction with endpoint by sex and differences between women and men when available
AVID (18.2 ± 12.2 months)	Cardiac arrest or syncopal VT if EF <40%	ICD or Class III AADs	1016	20	All-cause mortality	3.32 fold increased survival with ICD vs. AAD, $P = 0.02$	No sex-specific data reported
CIDS (2.9 years for amiodarone and 3.0 years for ICD)	Cardiac arrest or syncopal VT, or symptomatic VT if EF ≤35%	ICD or amiodarone	659	16	All-cause mortality	Non-significant decrease with ICD, (19.7% relative risk reduction; 95% CI 27.7–40%; $P = 0.142$)	No significant interaction by sex reported
CASH (57 ± 34 months)	Cardiac arrest or sustained VT	ICD or amiodarone or metoprolol	288	20	All-cause mortality	Non-significant decrease with ICD compared with the amiodarone and metoprolol groups combined [Crude death rates: ICD arm—36.4% (CI 26.9–46.6%)] and amiodarone + metoprolol—44.4% (95% CI 37.2–51.8%)	No sex-specific data reported
MADIT II (21 months)	Prior remote MI and EF ≤30%	ICD or conventional therapy	1232	15	All-cause mortality	The ICD was associated with a relative reduction in all-cause mortality of 31% (HR 0.69, $P = 0.016$).	No significant interaction by sex reported
DEFINITE (29.0 ± 14.4 months)	Non-ischaemic CM, EF ≤35%, PVCs or NSVT, NYHA Class I, II, or III HF	ICD or conventional medical therapy	916	29	All-cause mortality	ICD vs. optimal medical therapy: HR 0.65 (0.40–1.06), $P = 0.08$	No significant interaction by sex reported
SCD-HeFT (45.5 months)	Ischaemic and non-ischaemic CM, EF ≤35%, NYHA Class II or III HF	ICD or optimal HF medical therapy	1676 randomized to ICD or placebo	23	All-cause mortality	Lower mortality with ICD vs. placebo [0.77 (0.62–0.96) $P = 0.007$]	Non-significant interaction by sex: Women: HR 0.96 (0.58–1.61), Men: HR 0.73 (0.57–0.93)
MUSTT	CAD, EF ≤40%, unsustained VT and inducible sustained VT at EP testing.	No specific antiarrhythmic strategy (no AAD or ICD) compared with EP guided AAD, or ICD if AAD unsuccessful	704	10	Cardiac arrest or death from arrhythmia	Reduced primary endpoint with EP guided therapy which was accounted for by patients who received an ICD. Adjusted relative risk reduction: ICD patients compared with EP	No difference by sex in 2-year arrhythmic death or cardiac arrest event rate (Women: 9% Men: 12% adjusted HR 0.88); no difference in 2-year all-cause mortality rate: (Women:

Continued

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Table 7 *Continued*

Study	Enrollment population	Randomized therapy	Total enrollment	Women (%)	Primary outcome endpoint	Primary outcome in all patients	Interaction with endpoint by sex and differences between women and men when available
						guided/no ICD: 0.24 (0.13–0.45) and ICD patients compared with no antiarrhythmic (AAD or ICD) therapy: 0.27 (0.15–0.47). Results for all-cause mortality were similarly significant in favour of the ICD. $P < 0.001$	32% Men: 21% adjusted HR 1.51)
DEFINITE (29.0 ± 14.4)	NIDCM, EF ≤35, and PVCs	ICD or standard medical therapy	458	28.8	All-cause mortality	Non-statistical reduction in all-cause mortality (HR 0.65, 95% CI 0.40–1.06)	No significant interaction by sex reported
DANISH	NIDCM, EF ≤35%. NYHA II–IV (CRT allowed)	ICD or guideline directed HF medical therapy	1116	27.5	All-cause mortality	No significant difference in the primary endpoint of all-cause mortality (HR 0.87, 95% CI 0.68–1.12; $P = 0.28$)	No significant interaction by sex reported
DINAMIT (30 ± 13 months)	Recent MI (6–40 days), EF <35%, depressed HRV or elevated heart rate	ICD or conventional medical therapy	674	24	All-cause mortality	No significant difference for primary endpoint: 1.08 (0.76–1.44), $P = 0.66$	No significant interaction by sex reported
IRIS (37 months)	Recent MI (5–31 days), EF ≤40% and heart rate ≥90 b.p.m. and/or NSVT at ≥150 b.p.m. during Holter monitoring	ICD or conventional medical therapy	898	24	All-cause mortality	No significant difference for primary endpoint: HR 1.04 (0.81–1.35), $P = 0.78$	No significant interaction by sex reported

AAD, antiarrhythmic drug; AF, atrial fibrillation; AFL, atrial flutter; AVID, antiarrhythmics vs. implantable defibrillators; CAD, coronary artery disease; CASH, Cardiac Arrest Study Hamburg; CI, confidence interval; CIDS, Canadian Implantable Defibrillator Study; CM, cardiomyopathy; CRT, cardiac resynchronization therapy; CRT, cardiac resynchronization therapy; CV, cardiovascular; DEFINITE, Defibrillators in Non-ischaemic Cardiomyopathy Treatment Evaluation; DINAMIT, Defibrillation in Acute Myocardial Infarction Trial; EF, ejection fraction; EP, electrical programming; HF, heart failure; HR, hazard ratio; HRV, heart rate variability; ICD, implantable cardioverter-defibrillator; IRIS, immediate risk stratification improves survival; LV, left ventricular; MADIT, Multicenter Automatic Defibrillator Implantation Trial; MI, myocardial infarction; MUSTT, Multicenter Unsustained Tachycardia Trial; NIDCM non-ischaemic dilated cardiomyopathy; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart association; PVCs, premature ventricular complexes; SCD-HeFT, Sudden Cardiac Death in Heart Failure Trial; SR, sinus rhythm; VF, ventricular fibrillation; VT, ventricular tachycardia.

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patients in both treatment groups had CRT therapy. An interaction by sex on the primary endpoint was not observed.[260]

Registry studies and meta-analyses

Implantable cardioverter-defibrillator therapy was evaluated by sex in several studies using the US National Cardiovascular Data Registry (NCDR). While women had more co-morbidities, more device-related complications and higher risk of hospitalization for HF, adjusted mortality was not different,[259,261] and survival improved with ICD in both men and women.[262] In another large US registry survival did not differ between sexes after ICD implantation for primary or secondary prevention.[231] The Ontario, Canada ICD registry has provided information regarding ICDs in women. In 6021 patients referred for an ICD, only 21.4% were women. Of those who received an ICD, women were more likely to have more complications, both at 45 days and 1 year, although mortality rates were not different.[263]

The US National Inpatient Sample database[264] consisted of 311 009 patients who received a CRT-D or a CRT-P device 2006–12. Men were more likely to receive a CRT-D vs. a CRT-P compared with the women (88.6% vs. 80.1%, respectively). In concert with this observation in a French ICD registry sex differences in ICD or CRTD use and outcomes from 2002–12[265] were examined in 5539 men and women (15.1% of the cohort). More women had underlying NIDCM than men (60.2% vs. 36.6%, $P < 0.001$) and were more likely to receive CRT-P (61.0% vs. 52.5% in men). Women also were significantly more likely to also have a wide QRS (>120 ms), worse HF, and less AF. Women were significantly less likely to have appropriate, but not inappropriate shocks compared with the men (16 786 patient years follow-up). The investigators did not find a difference by sex for early complications or all-cause mortality.

In a very recent European Registry that combined retrospective data from 14 registries enrolling primary prevention ICD patients 2002–14, 5033 (19% females) patients with a mean age 63 years, were analysed for mortality, appropriate shocks and inappropriate shocks with a mean follow-up time of 33 months.[260] The aetiology of HF was ischaemic heart disease in 65% and 43% received a CRT-D. Mortality was significantly lower for women compared with men (13% vs. 20) with HR adjusted for age, cause of HF, LVEF, and presence of CRT of 0.65 (95% CI 0.53–0.79, $P < 0.0001$). After adjustment for these variables, the risk of first appropriate shock for females was 0.61 (95% CI 0.47–0.80, $P = 0.0003$). No sex-difference was noted for the first appropriate shock in CRTD vs. the ICD-only patients $P = 0.7578$. Finally in one meta-analysis of five RCTs,[205] women represented 22% of 7229 patients. Unlike men, women did not appear to experience a significant benefit from the ICD on all-cause mortality (HR for men 0.67, 95% CI 0.58–0.78; $P < 0.001$ and HR for women 0.78, 95% CI 0.57–1.05; $P = 0.10$). Women also had fewer appropriate ICD shocks (HR 0.63, 95% CI 0.49–0.82; $P < 0.001$). In a more recent meta-analysis of six RCTs including the DANISH trial women did not obtain a significant survival benefit from primary preventive ICDs compared with men.[266]

Key points

- Females are less likely to be referred for ICD therapy compared with males.
- Once referred, females are just as likely as males to receive an ICD. Women may have a lower appropriate use of ICD therapy
- Female ICD recipients have a higher complication rate related to the ICD implant compared with male recipients. Women may have a lower rate of appropriate ICD therapy
- Female recipients may have a lower all-cause mortality benefit compared with male recipients of an ICD.
- Women have represented a low percentage of patients enrolled into the randomized ICD trials.
- None of the randomized ICD trials were powered to examine sex-specific differences.
- Observational post hoc analyses by sex did not find a significant interaction by sex for the benefit of ICD therapy.

Consensus recommendations		Supporting references
Women who meet guidelines directed indications for ICD therapy should receive an ICD		42,267
Observational sex-specific differences in the benefits of ICD therapy are not currently supported by clinical trial results		42,267
Women may have a lower all-cause mortality benefit from primary prevention ICD therapy		
Observational data on sex-specific differences in the benefits of ICD therapy should not be considered for the risk stratification of patients who may be eligible for primary prevention ICD therapy		

Knowledge gaps

No RCT of ICD therapy has enrolled enough women establish whether the benefit of ICD therapy is equivalent to men. This is true for both primary and secondary prevention indications.

Recommendation for studies

Sufficient number of (or only) female patients should be included in RCTs and registries of ICD therapy to ensure adequate statistical power for analysis.

Future registries and RCTs need to have adequate numbers of female patients enrolled to determine sex-specific benefits.

Cardiac resynchronization therapy

Randomized trials

Although CRT is an established therapy for in NYHA II–IV HF with a reduced LVEF and electrical dyssynchrony[1,268] women have been under-represented the major RCTs and constitute 13–31% which makes it difficult to determine the interaction between CRT outcome and sex (*Table 8*). Only in the Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy (MADIT-CRT) study of mild HF patients a significant interaction with CRT was demonstrated in women. But none of the performed RCTs

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Table 8 **Women in cardiac resynchronization therapy randomized clinical trials**

Study and follow-up time	Enrollment Population	Randomized therapy	Total enrollment	Women, *n* (%)	Primary outcome endpoint	Primary outcome	Interaction with endpoint by sex
MIRACLE[269] (6 months)	Ischaemic or non-ischaemic CM NYHA III–IV, QRS >130 ms, EF <35%	CRT-P vs. VDI	453	145 (32)	NYHA class, 6 min-walk, Quality of life	Significantly Improved outcome with CRT Hospitalizations for worsening of HF HR 0.50, 95% CI 0.28–0.88; $P = 0.02$	Women more likely than men to be free from HF hospitalizations and death HR = 0.157 and had greater extent of reverse remodelling. Interaction with CRT not studied
COMPANION[270] (11.9–16.2) months	Ischaemic or non-ischaemic CM, NYHA Class III or IV HF, EF <35%, QRS >120 ms	CRT-P, CRT-ICD, or optimal HF medical therapy	1520	474 (33)	All-cause mortality + hospitalization for any cause	Improved outcome with CRT-ICD vs. optimal medical therapy: HR 0.80; $P = 0.01$, and with CRT-P vs. optimal medical therapy (HR 0.81, $P = 0.014$)	No significant interaction by sex; Women: 56% reduction in SCD with CRTD vs. OMT (HR 0.56, $P = 0.003$) both CRT and CRTD vs. OMT were similarly beneficial on mortality by sex
CARE HF[271] (29.4 months)	Ischaemic CM or NIDCM, NYHA Class III or IV HF, EF <35%, QRS >120 ms	CRT-P or optimal medical therapy	813	190 (26)	All-cause mortality plus unplanned CV hospitalization	Improved outcome with CRT-P; HR 0.63, 95% CI 0.51–0.77; $P < 0.001$	No interaction by sex; Men: HR 0.62, 95% CI 0.49–0.79 Women: HR 0.64, 95% CI 0.42–0.97
MADIT-CRT[272] (2.4 years)	Ischaemic or non-ischaemic CM, NYHA Class I or II HF, EF <30%, QRS >130 ms	CRT-ICD or ICD	1820	453 (25)	All-cause mortality or a non-fatal heart-failure event	CRT-ICD associated with improved outcome; HR 0.66; 95% CI 0.52–0.84; $P = 0.001$	Significant interaction by sex; Women: HR 0.37; 95% CI 0.22–0.6 Men: HR 0.76; 95% CI 0.59–0.97; $P = 0.01$ for the interaction
REVERSE[273] (12 months)	Ischaemic or non-ischaemic CM, NYHA Class I and II HF with LVEDD of >55 mm, EF <40%, QRS <120 ms	CRT-ICD randomly assigned to active CRT (CRT-ON; $n = 419$) or control (CRT OFF; $n = 191$)	610	112 (21)	1. HF clinical composite response2. LV end-systolic volume index	CRT ON was not associated with a significant difference in the primary endpoint compared with CRT OFF ($P = 0.10$) but with significant reduction in LV systolic volume index	No interaction by sex; Men: HR 0.69, 95% CI 0.43–1.11 Women: HR 0.75, 95% CI 0.26–2.19
RAFT[274] (40 months)	Ischaemic or non-ischaemic CM, NYHA class II or III HF, a EF <30%, QRS >120 ms pQRS >200 ms	ICD alone or an ICD plus CRT	1798	235 (17)	All-cause mortality or HF hospitalization	CRT-ICD associated with improved primary outcome: HR 0.75, 95% CI 0.64–0.87, $P < 0.001$)	No significant interaction with sex (trend toward greater benefit in women, $P = 0.09$)

CI, confidence interval; CM, cardiomyopathy; CRT, cardiac resynchronization therapy; CRT-P, cardiac resynchronization therapy pacemaker; CV, cardiovascular; EF, ejection fraction; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEDD, left ventricular end diastolic dimension; NIDCM, non-ischaemic dilated cardiomyopathy; NYHA, New York Heart Association; pQRS, paced QRS duration; SCD, sudden cardiac death.[269–274]

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was adequately powered to study sex-related differences in CRT outcome. Therefore, the results from the RCTs do not offer clear evidence of CRT benefit in relation to sex.

Registry studies, sub-studies of randomized clinical trials, and meta-analysis

In registry studies,[275] subgroup analysis,[276] and in a very large nationwide cohort[231] women derived a superior outcome from CRT to men. In the CERTITUDE cohort study female sex was independently associated with lower CRT-D (vs. CRTP), compared with men (Women OR 1.78, 95% CI 1.24–2.55; $P = 0.0018$), after considering potential confounders Women in CRT trials were of similar age as men but more often have underlying NICM, left bundle branch abnormality (LBBB), and less often ischaemic cardiomyopathy.[277–279] These factors are linked to a greater extent of reverse left ventricular remodelling by CRT[280] and hence potentially to a greater clinical benefit. Overall, the clinical benefit in terms of morbidity and mortality is no different in patients with ischaemic aetiology compared with NICM.[281] But in a recent meta-analysis the benefits of CRT on outcomes were similar for women and men with IHD, whereas for patients with NICM the observed benefit of CRT was greater among women.[282]

In guidelines recommendations patients with LBBB have a stronger class of recommendation for CRT than patients with wide QRS.[1,268] Guidelines also stress that sub-studies indicate that women derive a greater benefit from CRT than men.[1,268] Registry data clearly indicate that CRT response is greater in the presence of LBBB in women compared with men. In a study from Medicare of 144 642 CRT recipients,[283] LBBB was associated with a 26% mortality reduction in women (HR 0.74, 95% CI 0.71–0.77) and a 15% mortality reduction in men (HR 0.85, 95% CI 0.83–0.87) with a significant interaction ($P < 0.0001$) between sex and LBBB. These findings are supported by results from the NCDR[284] among 31 892 CRT-D recipients. In patients with LBBB, women had a 21% lower mortality risk than men (HR 0.79, 95% CI 0.74–0.84; $P < 0.001$); however, there was no sex difference in non-LBBB patients (HR 0.95, 95% CI 0.85–1.06; $P = 0.37$).

Women have shorter QRS duration than men and have LBBB at shorter QRS duration.[278] There is evidence that women benefit from CRT at smaller QRS duration than men. In MADIT-CRT,[285] women derived benefit at QRS ≥130 ms whereas men benefited at ≥140 ms. In large meta-analyses, women derived a survival benefit form CRT at already at QRS durations >120 ms whereas men only benefited at QRS durations >150 ms.[286] Lately, it has therefore been suggested that CRT indications should be different between men and women[287] but this has not yet been part of any guidelines recommendation.[1,268] Moreover there are many potential other reasons for why women may benefit more from CRT besides sex. In a recent study of only LBBB patients with NIDCM women benefited more from CRT than men. However, this difference disappeared when correcting for heart size.[288] In an individual patient data meta-analysis of five RCTs[282] women were shorter, had smaller left ventricular end diastolic dimension, more often LBBB, and less often CAD than men. Sex was not an independent predictor of outcome. For the composite outcome of mortality and HF related hospitalizations, only height and QRS duration, but not sex, were independent predictors of CRT benefit. Although this meta-analysis is not conclusive but hypothesis generating the results suggest that height may be new a factor in the consideration on CRT implantation in particular in patients with shorter QRS durations and that other yet unidentified factors may predict CRT response.

In conclusion, even though some evidence supports those women derive a greater benefit from CRT than men it is not clear whether this is due body stature, cardiac size, conduction delays, or aetiology or to female sex *per se*.

Cardiac resynchronization therapy utilization in women

There have been several reports on lesser CRT utilization in women both inside RCTs (*Table 8*) and in real life.[234,289] One such reason could be fear of more complications in women than in men but this has not been uniformly reported with no difference in an RCT[290] and higher risk of complications in the Danish Pacemaker and ICD registry[242].

In a HF registry study from Sweden, female sex was an independent predictor of non-referral for CRT as was high age[291] but underutilization of CRT in patients with an indication for therapy[278] was similar in women and men. Therefore, the assumption of large underutilization of CRT in women may not be correct, since it suggests that the prevalence of CRT indication is similar in women and men.

Women more often than men have HFpEF or mid-range LVEF (HFmrEF).[292] Though sub-studies of RCTs indicate that CRT benefit may extend to patients with mildly reduced ejections fractions[293,294] there is no guideline indication for CRT in such patients. The proportion of women with HF and LVEF <35% is clearly lower than in men.[292] It can therefore by hypothesized that a proper proportion of women in CRT trials should mimic LVEF distribution in HF registries and be in the order of 30%.[292]

Key points

- Women are more likely to benefit from CRT than men.
- Body size and sex should be considered when determining a CRT indication.
- Women are less likely to be referred for CRT than men.
- Fewer women than men have an indication for CRT since women more often have HFmrEF or HFpEF.
- The appropriate proportion of women indicated for CRT is therefore estimated to be 30%.

Consensus recommendation		Supporting references
Women with LBBB and QRS >150 ms and LVEF <35% despite optimal medical therapy should be referred for CRT therapy		1,268,282
Women with LBBB and QRS >130 ms and LVEF <35% despite optimal medical therapy are highly likely to respond to CRT and should be referred for CRT therapy		1,268,282

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Knowledge gaps

To further refine criteria for CRT implantation in women.

To study the value of separate inclusion criteria for women than men in RCTs.

To study if other measures such as height, heart size, and race are related to CRT outcome.

Recommendation for studies

Sufficient number of (or only) female patients should be included in RCTs of CRT therapy to ensure adequate statistical power for analysis.

Cardiac resynchronization therapies studies favouring inclusion of women.

Lead extraction

An increase in cardiac implantable electronic device implantations is being paralleled by an increase the requirement for safe transvenous lead extraction (TLE).[295] The most important risk factor for major complications in TLE are the number of leads requiring removal, long implantation time, ICD lead, operator experience, and female sex.[296] This was confirmed also by a European prospective controlled registry[297] (*Figure 10*). The possible explanation for female sex as a risk factor is BMI <25 kg/m^2 and thinner venous and myocardial walls. This means that the risk of inducing a tear in the wall is higher, particularly in the elderly.[298]

Traumatic injury to the tricuspid valve during TLE is more common in women and particularly with the use of tools like laser sheath and snare.[299] Whereas the tools used suggest the difficulty of TLE and the approximate degree of scar tissue ablation in order to remove the lead, women are more prone to complications during aggressive TLE. Use of the standard laser sheath seems to make extraction easier but is associated with a higher incidence of death or major complications.[300] Finally, operator experience is fundamental, even for taking in account the particular setting of the female patients.

Key points

- Female sex is a risk factor for major complications in lead extraction.
- Women are more prone to complications both for thinner CV walls that for a global frailty related to sex.
- A high volume centre with more experienced operators should be preferred to make lead extraction equally successful in women as in men.

Consensus recommendation		Supporting references
Women who require lead extraction should be treated in high volume centres and by experienced operators to increase the success rate of the procedure and to avoid reduce complications		297,298

Actions to increase women representation in trials

The poor representation of women in the majority of CV RCTs has long been recognized. It could be argued that the reason for including fewer women in RCTs reflect differences in disease prevalence and characteristics. Turning it around such reasoning also imply that women are different and that other criteria for a given therapy may apply and need to be identified. This is important knowledge in order to establish proper sex balance for a given therapy in RCTs and in real life.

In 2009, the ESC already focused on this subject in a document entitled 'Red Alert for Women's Hearts'[301] but as evidenced by this document not much has happened in the field of arrhythmia. Therefore, in 2013 EHRA introduced 'Women in electrophysiology' (WEP) committee with the intent of promoting sex balance in RCTs in order to provide generalizability of study results for both women and men.

Requirements for sex-balance by authorities

In the US, the situation is better. The United States National Heart Lung and Blood Institute were early to recognize the under-representation of women in clinical trials.[302,303] The mandate to ascertain proper female recruitment in clinical research therefore became public law. In 1990, the NIH/Office of Health and Human Services established the Office of Research on Women's Health (ORWH) to further strengthen efforts to promote women's health and sex-specific research,[304] Proposals for clinical research must include the investigators strategy to enrol sufficient women to allow an analysis of the outcome by sex. In 2012, the Food and Drug Administration (FDA) created an Office of Women's Health, to increase the focus on female enrolment in clinical trials.[305] In 2014, the FDA published an action plan to enhance the collection and availability of demographic subgroup data (http://www.fda.gov/downloads/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDASIA/UCHM410474.pdf).[306] This includes a commitment to work with industry to develop and share best practices for recruiting a broad representation of patients for clinical research supporting FDA medical product applications. In Europe, the European Medical Agency (EMA) in 2005 (EMEA/CHMP/3916/2005) came to the conclusion that gender is adequately represented in pivotal trial populations. However, it was acknowledged that estimates of disease prevalence in women vary between sexes with a delayed onset of heart disease in women than in men and that fewer women than men participated in early (Phase 1–2 studies). An update of this document from 2009 again found no need for separate trial guidelines on sex but highlights that dose-response data should be explored for demographic characteristics and that women are more susceptible to QT prolongation and may metabolize drugs differently. We do not share this perception and believe that the evidence in this consensus document calls for a new EMA assessment. A clear declaration that sex and gender balance is required in relation to disease prevalence will be helpful in the pursuit of sex-balanced enrolment in RCTs.

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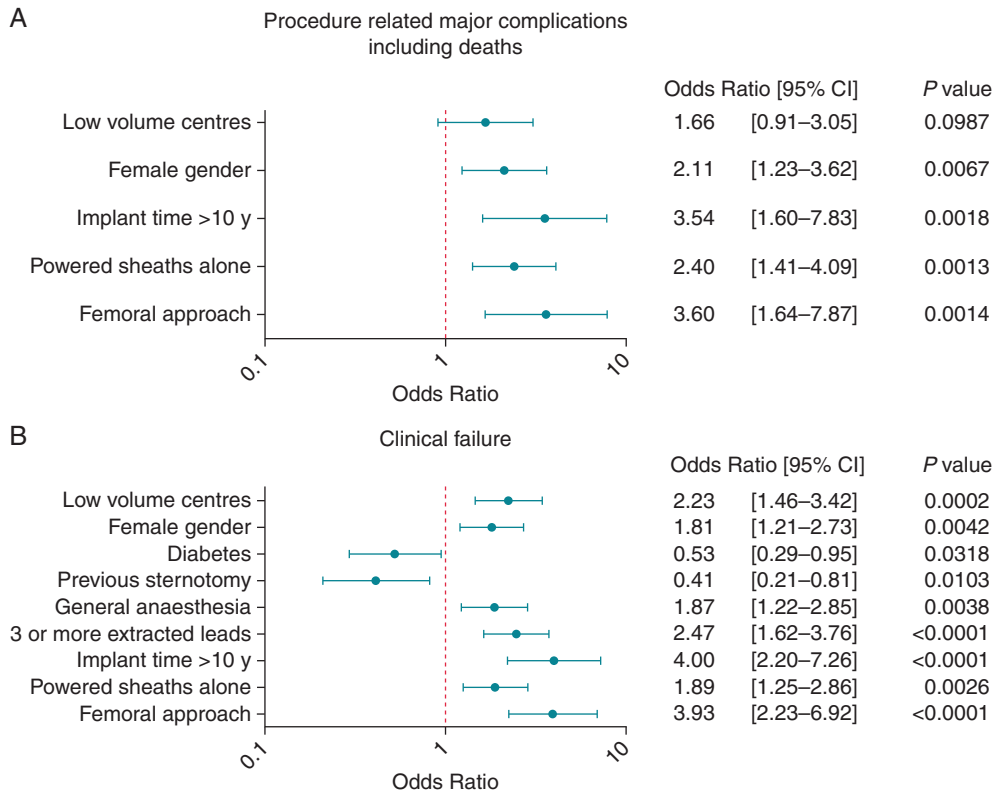

Figure 10 Female sex is a predictor of lead extraction related major complications (*A*) and clinical failure (*B*) in The European Lead Extraction ConTRolled (ELECTRa) study.[297]

Overcoming obstacles for female enrolment in clinical trials

It is important that women are offered trial participation as often as men and that the trial information is meaningful for both women and men. Exploratory analyses regarding potential obstacles for enrolling women, have included, apprehension related to the research process and randomization, preference of one potential investigative therapy, and perceived difficulties in completing trial testing and follow-up.[307]

To reduce barriers for participation in trials and to improve perception for trial participation the WIN-Her Initiative™ was initiated to increase female participation in device trials.[308] This industry sponsored multistep process included first the evaluation of experiences and attitudes toward CV research of women with CV disease by surveys and interviews. This information was then used to elaborate booklets, websites, and conversation templates with language and photos directed adapted to females and to be used by investigating physicians and research co-ordinators. Though this was not a study comparing male to females some interesting observations were made. Female patients wanted to learn more about clinical trial participation from their own personal cardiologist and/or primary care physician. Trial participation was more likely when these doctors were positive to the trial. Females wanted detailed information on the randomization process and potential risk and advantages. They also need more time to reflect on their decision and wanted to consult with family members and friends. This may reflect needs of all patients participating in trials. Interestingly however, female patients wanted more images of age-appropriate women including multigenerational family members in study materials. The women asked for that it was clearly stated that a study was designed to evaluate therapy in both women and men.

As a third step, the materials will be prospectively evaluated by questionnaires that explore decision-making, research expectations, and trial participation of female patients. The primary outcome is to determine whether the use of these clinical trial educational materials may improve general awareness of clinical research and ease the enrolment process aiming at least 35% female enrolment in the MADIT S-ICD (Multicenter Automatic Defibrillator Implantation Trial with Subcutaneous Implantable Cardioverter Defibrillator, NCT #02787785) and ASAP-TOO (Assessment of the WATCHMAN Device in Patients Unsuitable for Oral Anticoagulation, NCT # 02928497) trials.

Gender balance in committees such as steering committees of randomized clinical trial, guidelines, and scientific documents

Women increasingly ask for scientific evidence relevant to female sex. We are convinced that involving more female cardiologists and electrophysiologists in patient's treatment, in study design and study completion, in the committees of guidelines, and consensus documents is an important move towards improved knowledge for the female arrhythmia patients. Patient representation is increasingly

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recognized as an important aspect. The inclusion of females as patients' representants in guidelines committee elaboration and indeed in steering committees of clinical trials may help identify sex-specific implications of a given therapy and potential complications and benefits with regard to sex.

Key points

- A balanced proportion of men and women corresponding to the prevalence of the studied disease should be included in RCTs.
- To 'lower' the level of evidence required to support the use of treatment/diagnostics in women would be regressive rather than progressive. Therefore, we are unable to use green hearts for some recommendations because robust evidence is not available which calls for action.[3]
- Regular updates of therapy access and implementation should always be analysed by sex.
- Female cardiologists and patients should be adequately represented in associations, steering's committees of RCTs, in guidelines task forces, scientific documents to ensure gender equality.
- Female patients should be equally included as patientś representatives in such committee and guidelines elaboration.

Conclusions

In this consensus document we have summarized the current knowledge of sex-related differences in ECG and electrophysiological properties, arrhythmia incidence, aetiology and presentation. We provide sex related recommendation on diagnosis and treatment of various arrhythmias and response to therapies.

We also have illustrated knowledge gaps for each arrhythmia and suggest topics for new trials. Recommendations for management and therapies are given. In most randomised controlled too few women have been enrolled to make firm conclusions on a given arrhythmia therapy. We make suggestions how to improve enrolment to ensure power for firm conclusions in relation to female sex.

We also call for greater awareness of sex-imbalance and actions to prevent it when planning and performing clinical trials Such suggestions include female representation in guidelines committees, steering committees, in guidelines implementation programs and in the preparation of information materials of therapies and trials.

Ultimately, regulations from organisations such as the European commission and EMA regarding obtaining a better sex-balance in trials on cardiovascular disease including arrhythmia are warranted.

Acknowledgements

The authors thank EHRA Scientific Documents Committee: Gregory Y.H. Lip, Laurent Fauchier, David Arnar, Carina Blomstrom-Lundqvist, Irina Savelieva, Zbigniew Kalarus, Gulmira Kudaiberdieva, Georges H. Mairesse, Jesper Hastrup Svendsen, Vassil B. Traykov, Vanessa Meyen (EHRA).

Declaration of interest:

U.B.-G.: Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. from healthcare industry. Abbott : CRM (2017); Medtronic : CRM (2017); Biotronik : CRM (2017).

M.G.B.: Direct Personal payment: Speaker fees, Honoraria, Consultancy, Advisory Board fees, Investigator, Committee Member, etc. from healthcare industry. Boston Scientific : S-ICD (2017).

B.C.: Research funding (departmental or institutional) from healthcare industry. Merck Sharp & Dohme (Spouse) : Anacetrapib (Phase III RCT) (2017); Merck Sharp & Dohme (Spouse) : Inclisiran (Phase III RCT) (2017); Roche Diagnostics : Provides assays to evaluate the aetiology of AKI in rosuvastatin-allocated patients and biomarkers of incident AF in the STICS trial at no cost to the investigators (2017); Merck Sharp & Dohme (Spouse) : To cover the cost of sample storage in China for the China Kadoorie Biobank (2017).

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Research funding (personal). Spectrum Dynamics : Nuclear Imaging (2017).

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T.F., J.S.,: Nothing to be declared.

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