CJC Open 6 (2024) 503–516

Review

Unique Aspects of Women's Valvular Heart Diseases: Impact for Diagnosis and Treatment

Andréanne Powers, MD,[a] Nicolas Lavoie, MD,[a,b] Emma Le Nezet, MSc,[a] and Marie-Annick Clavel, DVM, PhD[a]

[a] *Institut Universitaire de Cardiologie et de Pneumologie de Québec—Université Laval, Québec, Québec, Canada*

[b] *Faculty of Medicine, McGill University, Montréal, Québec, Canada*

ABSTRACT

Valvular heart diseases (VHDs) are a major cause of cardiovascular morbidity and mortality worldwide. As degenerative and functional mechanisms represent the main etiologies in high-income countries are degenerative and functional, while in low income countries etiologie is mostly rheumatic. Although therapeutic options have evolved considerably in recent years, women are consistently diagnosed at later stages of their disease, are delayed in receiving surgical referrals, and exhibit worse postoperative outcomes, compared to men. This difference is a result of the historical underrepresentation of women in studies from which current guidelines were developed. However, in recent years, important research, including more female patients, has been conducted and has highlighted substantial sex-specific differences in the etiology, diagnosis, and treatment of VHDs. Systematic consideration of these sex-specific differences in VHD patients is crucial for providing equitable healthcare and optimizing clinical outcomes in both female and male patients. Hence, this review aims to explore implications of sex-specific particularities for diagnosis, treatment options, and outcomes in women with VHDs.

RÉSUMÉ

Les valvulopathies sont une cause majeure de morbidité cardiovasculaire et de mortalité dans le monde. Les mécanismes dégénératifs et fonctionnels représentent maintenant les principales étiologies dans les pays à revenu élevé, mais la maladie valvulaire rhumatismale demeure très prévalente dans les pays à revenu faible. Par ailleurs, même si les options thérapeutiques ont évolué depuis quelques années, les femmes reçoivent systématiquement leur diagnostic à des stades plus avancés de la maladie, sont orientées plus tard en chirurgie et les issues postopératoires sont moins favorables par rapport aux hommes. Cette différence s'explique par une sous-représentation historique des femmes dans les études sur lesquelles reposent les lignes directrices actuelles. Cependant, des études importantes réalisées ces dernières années ont mis au jour des différences substantielles entre les sexes en ce qui a trait à l'étiologie, au diagnostic et au traitement des valvulopathies. Il est essentiel de tenir compte des différences selon le sexe chez les patients atteints d'une valvulopathie pour fournir des soins de santé équitables et optimiser l'issue clinique tant chez les femmes que chez les hommes. Cette analyse vise donc à explorer les implications des particularités selon le sexe en ce qui concerne le diagnostic, les options thérapeutiques et les issues chez les femmes atteintes de valvulopathies.

Lay Summary

Valvular heart diseases (VHDs) are a major cause of disease and death. Each of the 4 valves can either "leak" because they fail to close properly, be too "narrow" for proper blood flow, or both. Even with improved treatments, female patients are diagnosed and referred for treatment later than male patients and have worse outcomes than men after surgery. This review explores sex-specific differences that are important for better diagnosis, treatment, and outcomes in women with VHDs.

Valvular heart diseases (VHDs) are one of the leading causes of cardiovascular morbidity and mortality worldwide. Even though rheumatic valve disease remains the most prevalent form of VHD in low-income countries, degenerative and functional diseases have become predominant in high-income countries due to the wide access to group A Streptococcus treatment and significant improvement in socioeconomic conditions.[1,2] As the population ages, the burden of degenerative heart valve disease is expected to grow substantially in the upcoming years. Therapeutic options, which have evolved considerably in the past few decades, rely mostly on interventions, either surgical or transcatheter, as no

Received for publication August 15, 2023. Accepted October 15, 2023.

Corresponding author: Dr Marie-Annick Clavel, Institut universitaire de cardiologie et de pneumologie de Québec, 2725 Chemin Sainte-Foy, Québec city, Québec G1V-4G5, Canada. Tel.: +1-418-656-8711 x2678; fax: +1-418-656-4715.

E-mail: Marie-Annick.Clavel@criucpq.ulaval.ca

See page 513 for disclosure information.

https://doi.org/10.1016/j.cjco.2023.10.017

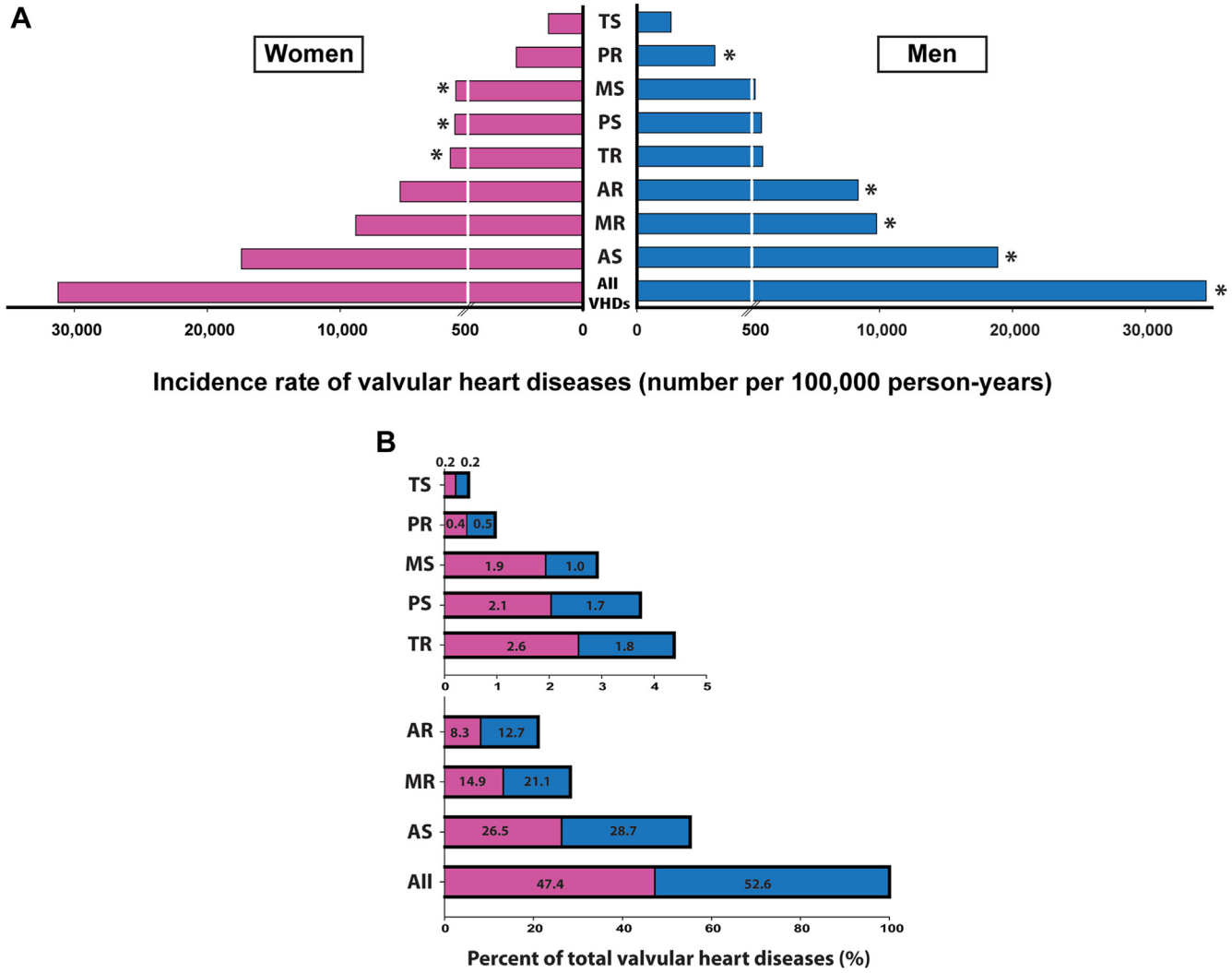

Figure 1. Incidence of valvular heart diseases (VHDs) according to the sex of the patient.[5] (A) Incidence per 100,000 person-years of VHDs and (**B**) relative frequencies in % of VHDs in Sweden, according to the sex of the patients. The **pink bars** represent the data for women and the **blue bars** represent the data for men. *Significantly different incidence of VHDs between sexes. AR, aortic regurgitation; AS, aortic stenosis; MR, mitral regurgitation; MS, mitral stenosis; PR, pulmonary regurgitation; PS, pulmonary stenosis; TR, tricuspid regurgitation; TS, tricuspid stenosis. From Clavel et al.[5](The data presented in this figure are obtained from the study of Andell et al.[4]) with permission from BMJ Publishing Group Ltd.

pharmacologic treatment has exhibited beneficial outcomes on valvular disease progression in human subjects to date.[3]

In high-income countries, the vast majority (~70%) of VHDs are diagnosed in patients aged ≥ 65 years, except for pulmonary valve disease. Despite the belief that VHDs affect mostly male patients, 47% of the patients diagnosed with any VHDs are female, with a slightly lower incidence rate of any VHDs in female compared to male patients, except for tricuspid regurgitation and mitral stenosis (Fig. 1).[4-6]

Although many studies have underrepresented female patients, major differences regarding valvular disease pathophysiology, presentation, referral for intervention, treatment, and outcomes of male vs female patients have been documented in recent years. We here sought to explore sex-specific differences in clinical presentation, management, and therapeutic outcomes of the most common degenerative or functional VHDs in adults—respectively, aortic stenosis (AS), chronic aortic regurgitation (AR), mitral regurgitation (MR; both organic and functional), and tricuspid regurgitation (TR).

Aortic Stenosis

Prevalence, etiology, and pathophysiology

Calcific AS is the most common VHD in industrialized countries, with a prevalence of 0.4% in the general population, and of up to 1.7% in adults older than 65 years.[7] The number of incident patients older than 65 years hospitalized with AS is shown to be similar for men vs women.[6] However, the incidence is higher in men before that age, due to the higher prevalence of bicuspid aortic valve in men, with an estimated 3 cases in men for every 1 case in women.[8,9]

AS physiopathology is characterized by progressive valve leaflet stiffening and remodeling caused by a complex process

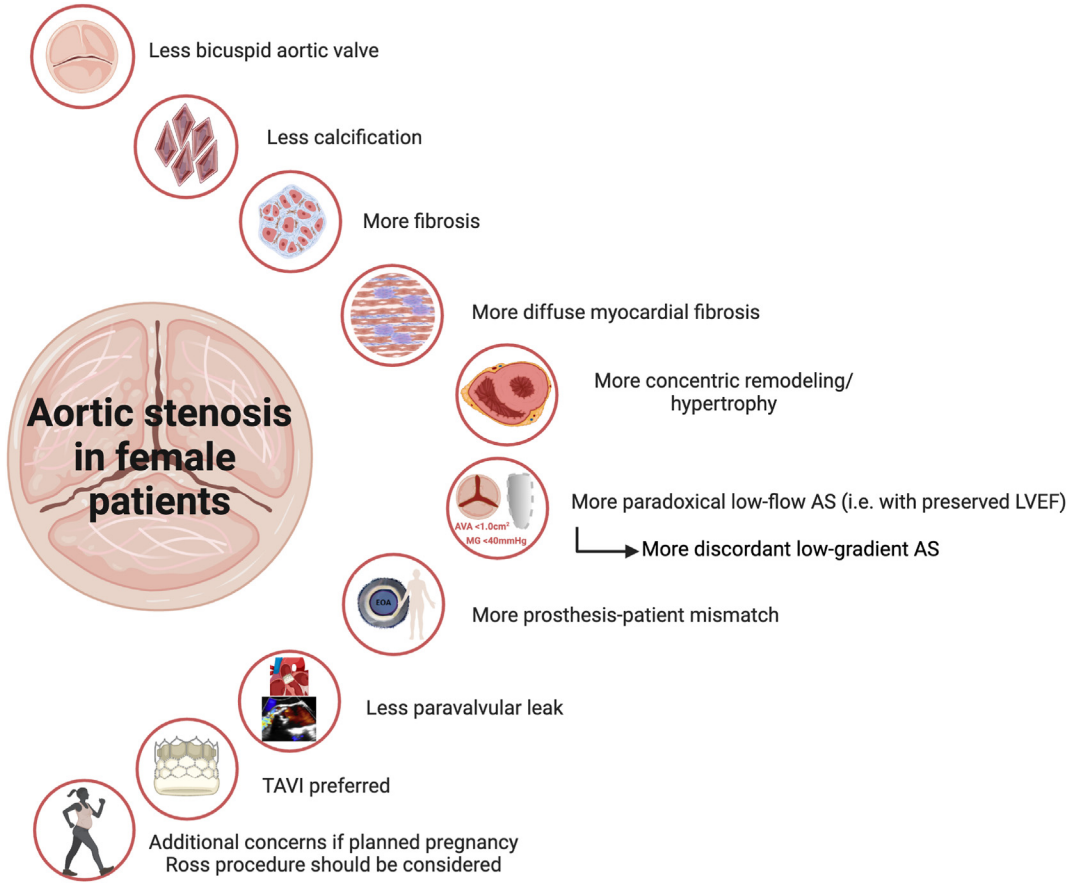

Figure 2. Principal features of aortic stenosis (AS) in women. LVEF, left ventricular ejection fraction; TAVI, transcatheter aortic valve implantation.

that includes a primary injury, lipid deposition, inflammation, and mineralization. For the same hemodynamic severity of stenosis, male patients present with more-calcified aortic valves than female patients, who are shown to exhibit higher levels of fibrosis and dense connective tissue.[10,11] In addition to biomechanical alterations of the aortic valve, the narrowed valve area increases afterload, resulting in left ventricular eccentric or concentric hypertrophy. An interesting sex-specific adaptation of the left ventricle (LV) occurs, with more concentric hypertrophy in female patients (Fig. 2) and more eccentric hypertrophy in male patients.[12] This myocardial adaptation, which initially maintains wall stress and preserves LV function, is deleterious in the long-term. In fact, capillary networks do not expand sufficiently to meet the high oxygen demands of increased afterload and myocardial mass, which results in myocyte apoptosis, fibrosis, and subsequent scarring.[13]

Presentation and diagnosis

Assessment of AS severity is performed using Doppler echocardiographic parameters, with values of mean gradient $>$ 40 mm Hg, peak aortic jet velocity $>$ 4 m/s, and aortic valve area $<$ 1.0 cm^2 indicating severe disease. As the ventricle presents a concentric remodeling and/or hypertrophy in women, more women will present with low-flow AS despite having a preserved left ventricular ejection fraction (LVEF; ie, paradoxical low flow—Fig. 2). This presentation has 2 major implications for women's diagnosis and referral for intervention. First, the LVEF threshold of 50% to assess LV systolic dysfunction is probably too low in women. An interesting finding in recent studies is that in both male and female grouped patients cohorts, the LVEF threshold associated with mortality is probably more than 55%-60%.[14,15] Second, discordance between the aortic valve area (in the severe range) and the mean gradient (in the moderate range) occurs frequently in female patients, is often associated with low flow, and it is insidious, as LVEF remains normal or supra-normal. Thus, both peak aortic jet velocity and/or gradient and aortic valve area must be evaluated and considered, as opposed to the proposed approach in the American guidelines, which is based mostly on velocity.[16] These 2 points may both contribute equally to underdiagnosis of severe AS in women and delay or denial of aortic valve replacement (AVR) in women. In North America, women are less likely to be referred to a cardiologist and to undergo diagnostic tests, and AVR is performed in women at rates significantly lower than those for men,[17] especially if echocardiography parameters are discordant.[18]

To avoid such delay, aortic valve calcification must be measured by computed tomography if echocardiographic parameters are discordant. As female patients develop less aortic valve calcification, but more valvular fibrosis, than men for the same level of AS severity,[10,11] sex-specific

thresholds of aortic valve calcification measured by computed tomography to identify severe AS have been proposed (ie, 1200 or 1300 Agatston units in female patients, and 2000 Agatston units in male patients; Fig. 2).[19,20] These thresholds are included in the current American and European guidelines.[21,22] Moreover, despite women having less calcification and more fibrotic remodeling than men, regardless of valve phenotype or age, this difference appears to be even more important in young patients.[11] Indeed, in young bicuspid female patients, aortic valve calcification is often lower than expected for a female patient and is sometimes totally absent, even in cases of severe AS.[11,23]; thus aortic valve calcification measured by computed tomography should be used with caution. Also, if follow-up echocardiograms are available, a LVEF decrease of 10% should raise concern, even if the LVEF is 60%. If follow-up examinations are not available, global longitudinal strain (GLS) could be used to assess systolic dysfunction. Indeed, an impaired GLS of below 15 (in absolute value) has been associated with worse outcome in asymptomatic AS patients.[24]

The classic triad of symptoms in AS consists of angina, dyspnea, and syncope, with a poor prognosis (2-3—year survival) when one of these manifestations arises and no intervention is performed. An interesting difference is that female patients present more often with shortness of breath, whereas males more often present with angina. This difference may be due to the higher incidence of coronary artery disease in male patients.[25] These differences in presentation could also contribute to the delay in treatment of women, due to their having "less severe" or "less dramatic" symptoms. The use of type-B natriuretic peptide (BNP) or N-Terminal pro-BNP level may help in determining an association of shortness of breath with cardiac diseases; however, the expected value must be used, as the levels of both BNP and N-Terminal pro-BNP increase with age and are higher in women.[26] Serial BNP assessments (every 6 or 12 months) can also be very useful, as they avoid the limitation of mandatory use of the expected value, by using patient's baseline values as a control.[27] Indeed, patients with higher annualized BNP changes have a greater risk of cardiac events, despite having similar baseline values.[27]

Therapeutic options

As no pharmacologic treatment has been proven to be effective in preventing AS or halting its progression, AVR, either surgical or percutaneous, is required once AS is severe and the patient has become symptomatic or has impaired LV function (class I indications).[16] Male sex is clearly associated with a higher frequency of early AVR, despite the fact that women exhibit more symptoms. Moreover, in patients presenting with severe AS and class I indications for AVR in accordance with echocardiographic parameters, a significantly higher proportion of men than women are referred for evaluation by a cardiac surgeon.[28,29] The higher incidence of AVR in male patients may be related in part to the higher occurrence of concomitant surgery at the time of AVR, such as coronary artery bypass grafting, aorta repair, or aorta replacement (either associated or unassociated with bicuspid aortic valve). However, in patients with similar evaluation and comorbidities, women are still referred to AVR less often than men, especially in the group of patients with discordant echocardiographic findings.[18]

In adults, intervention options include surgical AVR (SAVR) and transcatheter AVR (TAVR). The consensus in the literature is that male patients tend to benefit more than female patients from surgical approaches when undergoing AVR.[30-32] After SAVR, women have higher rates than men of in-hospital mortality, non-home discharge, and long-term mortality.[31-33] The clear disparity in outcomes can be attributed in part to the worse preoperative characteristics in the women, who were older and had a poorer health status at baseline than the men.[18,31] Moreover, concentric hypertrophy is associated with significantly higher mortality compared with other patterns of myocardial remodelling, in women specifically.[12] Accordingly, some specific features of AS in women are associated with a worse outcome after SAVR, such as low-flow AS with preserved LVEF.[34] Women also present with a smaller aortic annulus than that of men, for the same body size, which makes them more vulnerable to prosthesis—patient mismatch (PPM; Fig. 2). PPM occurs when the effective orifice area of the prosthesis is too small in relation to the patient's body size, and consequently, to their cardiac output requirements. The prevalence of PPM following SAVR is 10%-20% and 20%-70%, for severe and moderate PPM, respectively. The impacts of PPM following AVR include lower regression of left ventricular myocardial hypertrophy, less recovery of coronary flow reserve, less regression of MR, less improvement in functional class, worse exercise capacity, increased incidence of late cardiac events, increased bleeding complications, increased incidence of bioprosthesis structural valve deterioration, and negative impact on short- and long-term survival.[35,36]

An interesting finding is that TAVR may be able to overcome some of these specific features of AS. Occurrence of severe PPM after TAVR is about 1%, and of moderate PPM is about 10%,[37] and TAVR is superior to SAVR for PPM prevention, especially in small aortic annuli.[38-40] Self-expanding valves could be superior to balloon-expandable valves in terms of PPM, as their positioning is supra-annular.[41] Also, given that the TAVR procedure is less invasive, it may be preferable for patients with low flow and reduced or preserved LVEF, as they have impaired diastolic function, decreased GLS, and reduced stroke volume index.[42,43] In addition, the quantity of aortic valve calcification has been associated with worse outcomes after TAVR,[44,45] such as increased paravalvular leak and greater need for a permanent pacemaker; also, as discussed earlier, women have less calcification than men. This difference may explain the fact that despite TAVR being associated with a greater frequency of both paravalvular leak and permanent pacemaker implantation than SAVR, their incidence is lower in women than it is in men.[46-49]

In high-risk female patients, TAVR is associated with lower late mortality than SAVR (28.2% vs 38.2% at 2 years), especially when TAVR is performed through a transfemoral access (Fig. 2).[50] A meta-analysis of randomized controlled trials comparing survival in severe AS patients undergoing SAVR or TAVR showed that in women, TAVR has a 26% to 31% lower odds of mortality than does SAVR.[51] Women now represent more than 50% of patients undergoing TAVR, and this percentage is expected to increase with the additional

Table 1. Comparison of the most commonly used frailty scales in the context of aortic valve replacement

Frailty scale	Items	Cutoff	Pros	Cons
Essential Frailty Toolset (EFT)	- Chair rise time (5) - Cognitive impairment (MMSE or Mini-Cog test) - Serum hemoglobin - Serum albumin	≥ 3/5	- Objectiveness - Multiple domains assessed - Quick to perform (if Mini-Cog Test used instead of MMSE)	- Time-consuming
Short Physical Performance Battery (SPPB)	- Gait speed - Chair rises - Side-by-side/semi-tandem/tandem stand	≤ 8/12	- Objectiveness	- Few domains assessed - Modest specificity - Time-consuming
Fried Scale	- Gait speed - Grip strength - Weight loss (self-reported > 10% unintentional in the last year) - Exhaustion (self-reported) - Inactivity (calories spent/wk)	≥ 3/5	- Multiple domains assessed	- Patient-reported items introduces potential recall bias - Specialized equipment required (grip strength) - Time-consuming
Rockwood Clinical Frailty Scale (CFS)	- Symptoms (self-reported) - Mobility (self-reported) - Inactivity (self-reported) - Exhaustion (self-reported) - Disability for ADLs - Instrumental ADLs	≥ 5/9	- Reasonable interrater reliability - Does not require extensive training	- Lacks objectivity
Bern Scale	- Gait speed - Cognition (MMSE) - Nutrition (Mini Nutritional Assessment) - Instrumental ADLs - Basic ADLs - Instrumental ADL disability	≥ 3/7	- Objectiveness - Multiple domains assessed - Does not require specialized equipment	- Time-consuming
Columbia score	- Gait speed - Grip strength - Serum albumin - ADLs disability (Katz ADL survey)	≥ 6/12	- Objectiveness - Quick to perform - Does not rely on self-reported items	- Specialized equipment required (grip strength) - Time-consuming

ADL, activity of daily living; MMSE, Mini Mental State Examination.
Adapted from Chuang et al.[59] with permission from Elsevier.

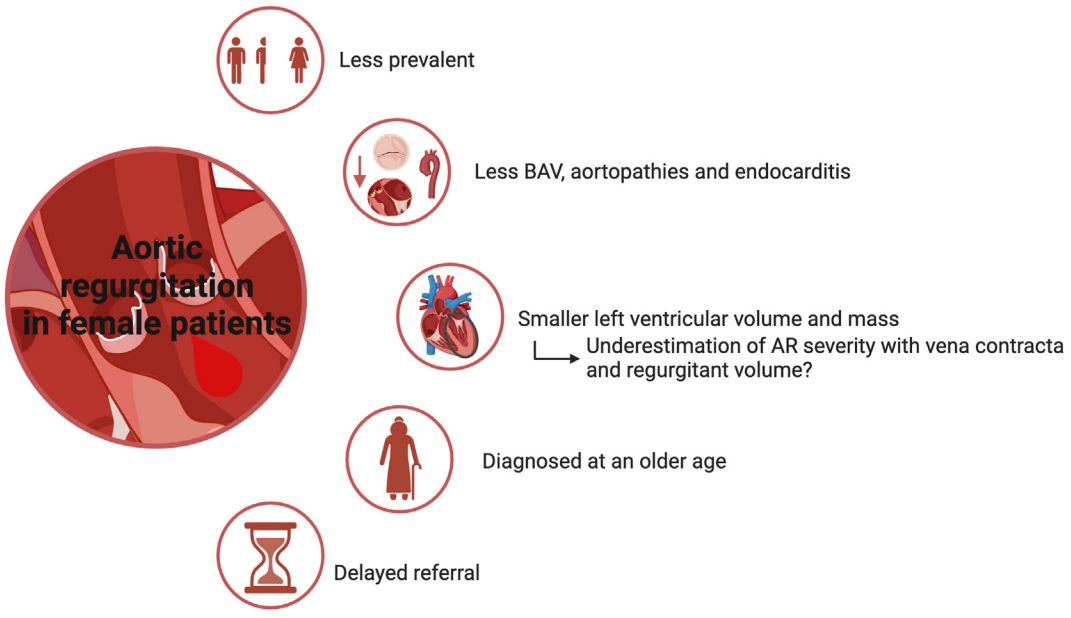

Figure 3. Principal features of aortic regurgitation (AR) in women. BAV, bicuspid aortic valve.

evidence corroborating the superiority of TAVR over SAVR in female patients with severe AS[52] and the results of the ongoing **R**andomized Researc**h** in Wom**e**n All Comers W**i**th **A**ortic Stenosis (RHEIA) trial.[53]

AVR in female patients planning pregnancy

In women planning pregnancy and in whom AVR in necessary, several concerns need to be addressed. In young patients, a mechanical prosthesis is often the first choice, given the increased durability of the device compared to that of a bioprosthesis, which usually lasts 10-15 years before a reoperation is necessary. In such patients, long-term anticoagulation is required to avoid thrombotic events, but the medication also increases the risk of bleeding. Despite anticoagulation being possible in pregnancy by replacing warfarin, which is associated with higher fetal mortality, by heparin, which is less effective, it is less than ideal.[54] Thus, if pregnancy is minimally anticipated before AVR, a mechanical valve should be avoided, as no anticoagulation medication is optimal for both mother and fetus.[55] The Ross procedure is an especially attractive option, as it is not accompanied by either need for long-term anticoagulation or increased concerns for bioprosthetic valve durability, as accompanies use of a bioprosthesis in young patients (Fig. 2).[56] This operation, devised by Donald Ross in 1967, allows for the native aortic valve to be excised and replaced by the patient's own pulmonary valve. Allograft tissue is then positioned in the low-pressure pulmonary position. The Ross procedure is associated with a lower reintervention rate and better survival than other AVR options in high-volume centres.[57] However, the procedure has its own challenges, given that it carries a risk of converting a single-valve disease into a double-valve disease, potentially exposing patients to complex reoperations, with a significant rate of reintervention mortality.[57,58] Thus, an important point to highlight is that the Ross procedure is a technically complex procedure and its outcomes are highly dependent on surgeon expertise and hospital surgical volumes.

Frailty indexes

When discussing sex differences in baseline presentation for AVR, frailty, associated with poor functional recovery potential in geriatric patients, is a recurring theme. In fact, although several scales can be used to measure frailty, a lack of consensus remains regarding their accuracy and standardization. In fact, the prevalence of frailty varies greatly, depending on the scale used by physicians to measure it (Table 1).[59] Thus, with women consistently being evaluated as having higher frailty scores, compared to those of men, bias in the assessment of frailty could be in part responsible for the lower referral rates to AVR of female patients. The Essential Frailty Toolset (EFT), a standardized frailty score that has been demonstrated to be the strongest predictor of death at 30 days and at 1 year following TAVR, as well as worsening disability at 1-year post-TAVR, seems to outperform other frailty scales and is therefore recommended in this setting.[60]

Implications

Given the complexity of factors that need to be taken into consideration when selecting an appropriate intervention for severe AS patients, a comprehensive assessment by a specialized heart team should be performed to ensure that an appropriate individualized decision is made. Sex-specific differences in pathophysiology and adaptive mechanisms are also crucial to consider in identifying the best point for intervention to produce maximal benefit. Accordingly, the paradoxical low-flow low-gradient pattern exhibited in a significant subset of female patients should be given greater recognition in clinical practice, to ensure that women have access to optimal therapeutic options even when presenting with a preserved LVEF.

Aortic Regurgitation

Prevalence, etiology, and pathophysiology

AR is a common VHD with an estimated prevalence of 4.9% and 0.5%, when including either any degree of AR or solely moderate/severe AR, respectively.[61] AR is more frequently observed in men than in women (13% vs 8.5%; Fig. 3), and its incidence increases with age.[62] In high-income countries, the main etiology of AR is degenerative, especially in patients with bicuspid aortic valve (BAV), which explains why the disease is more prevalent in male patients. Indeed, BAV affects approximately 0.5%-2% of the population, with a 1:3 female-to-male patient ratio (Fig. 2). An interesting finding is that the most frequent type of degeneration of the BAV in men is AR, whereas AS is the most common in women.[63,64] (BAV is also often associated with dilatation of the aortic root or of the proximal ascending aorta, which makes patients more susceptible to secondary AR. In patients with BAV, men show larger diameters of the aortic root structures, and of the ascending aorta, and thus have more aortopathies (Fig. 3).[65] Additionally, patients with AS often have concomitant AR, with about 75% of patients with a primary diagnosis of AS exhibiting some degree of AR.[66]

The disease is characterized by the reflux of blood from the aorta to the LV during diastole, reducing the effective stroke volume and resulting in volume overload of the LV. AR can be the consequence of abnormalities of either the aortic leaflets or the structures supporting them, mainly the aortic root and the aortic annulus. Mild and moderate AR are generally well tolerated, and they are benign if LV dimensions remain within normal range. However, as the severity of the disease increases, the LV undergoes adaptive remodelling. Eccentric hypertrophy is the most predominant pattern, with LV cavity dilatation, which initially preserves stroke volume and ventricular function, but later results in systolic dysfunction.[67] An interesting finding is that female patients have smaller ventricular volumes and mass, compared to those of men, even when measurements are indexed to body surface area (BSA; Fig. 3).[68] However, this difference seems to be present mainly in patients with mild AR.[68]

Presentation and diagnosis

The first-line assessment of AR is echocardiography, which allows imaging of valve morphology and hemodynamics, as well as visualization of the aortic root and ascending aorta. LV size and systolic function are also assessed, as they are crucial criteria for referral to intervention. AR is considered severe when conditions are as follows: the Doppler jet width is

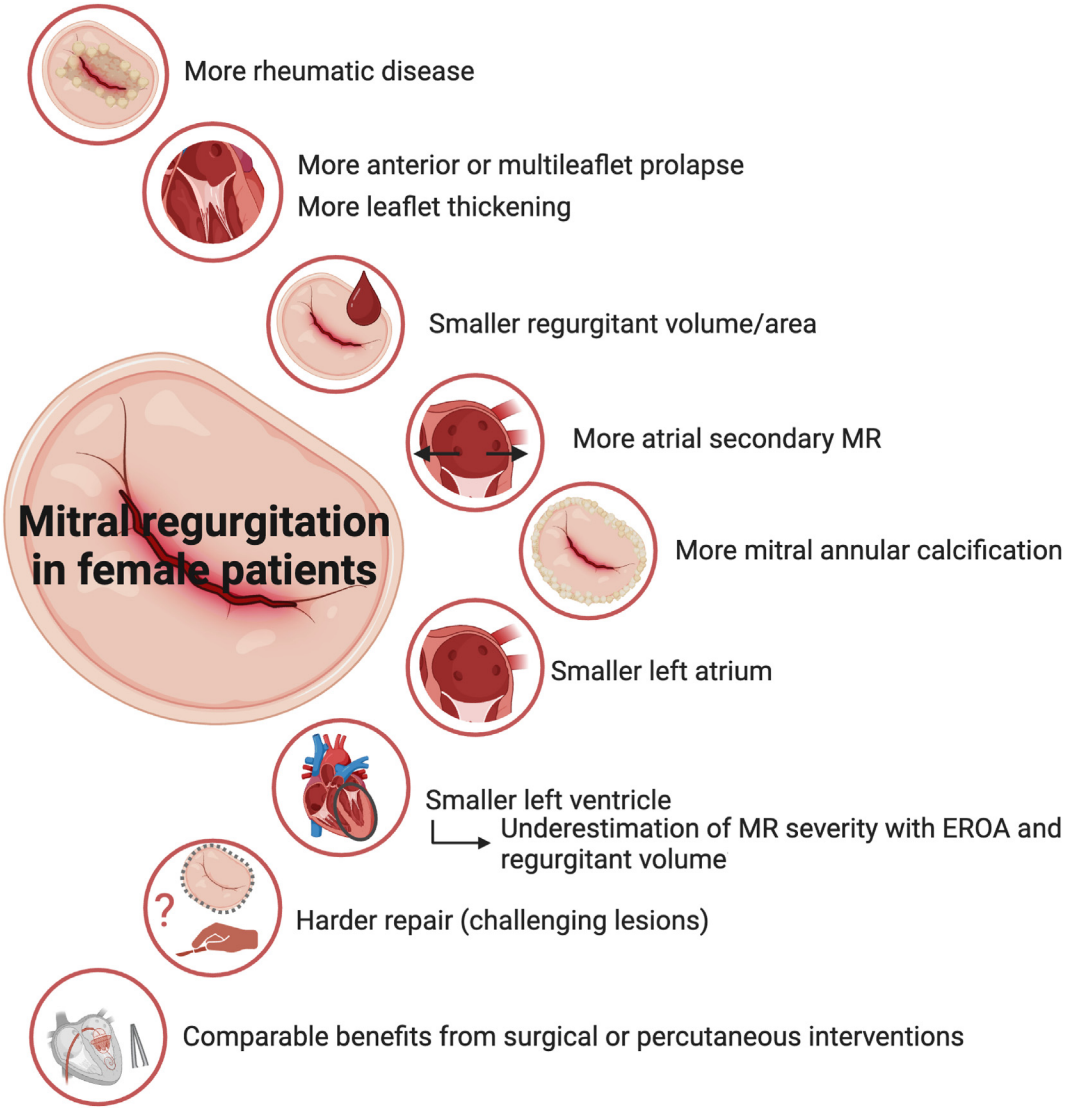

Figure 4. Principal features of mitral regurgitation in women. EROA, effective regurgitant orifice area; MR, mitral regurgitation.

$\geq$ 65% of LV outflow tract; the vena contracta is superior to 0.6 cm; the regurgitant volume is $\geq$ 60 mL/beat; the regurgitant fraction is $\geq$ 50%; and the effective regurgitant orifice area is $\geq$ 0.3 cm^2.[16] Diagnosis of severe chronic AR also requires evidence of LV dilatation.[16] As the female LV is smaller than the male LV,[69] absolute measurement of the vena contracta and the regurgitant volume probably underestimates AR severity in women (Fig. 3); thus, the regurgitant fraction should be preferred in female patients.

Therapeutic options

Compared to male patients, female patients consistently present for aortic valve surgery with more advanced symptoms and exhibit a higher incidence of postintervention mortality. This difference is a result of the later referral of women to both tertiary-centre evaluation and intervention (Fig. 3), as evidence shows that worse outcomes for female patients with AR cannot be explained by biological idiosyncrasies.[70] However, an important point to note is that post—aortic valve surgery survival rates for women have greatly improved in recent years.[70]

Regarding the timing of intervention, aortic valve surgery is indicated in symptomatic patients regardless of their LV systolic function. In asymptomatic patients with chronic severe AR and LVEF $\leq$ 55%, surgery is indicated if no other cause for systolic dysfunction is identified. Intervention is also recommended in patients with severe AR who are planning to undergo cardiac surgery for another indication.[16] Furthermore, the cutoff point of the LV end-systolic diameter for optimal postoperative survival is indexed to BSA (< 25 mm/m^2).[16,22] This approach is a significant improvement, as previous guidelines did not take into account patients' body size, obviously resulting in significantly lower intervention referral rates for female patients, possibly for more-severe AR, given that female patients have smaller hearts.[71]

Although the rate of TAVR has skyrocketed in the context of AS in recent years, its role in isolated chronic AR is less

clear. Indeed, the dilatation of both the aortic annulus and the aortic root, often associated with AR, limits the use of TAVR in this subset of patients, as this dilatation increases the risk of prosthesis migration and significant paravalvular leak.[72,73] Hence, TAVR is considered mainly in carefully selected patients who have pure severe AR and prohibitive surgical risk.

In asymptomatic patients with chronic AR, medical therapy is recommended in hypertensive patients, to reduce afterload.[16] However, no evidence supports the use of vasodilating drugs to reduce severity of AR in the absence of arterial hypertension.[16] Diuretics and vasodilators are the drugs of choice, and they also can be used to manage symptoms in patients deemed inoperable. The most used treatments include angiotensin-converting enzyme (ACE) inhibitors, and calcium-channel blockers, classically nifedipine.[3,74] No sex-specific management has been proposed yet.

Implications

AR is an undertreated VHD, but this is even more true for female patients. Indeed, there are clear disparities between male and female patients in their referral and management for severe symptomatic AR, even though current guidelines are unequivocal regarding the benefits of surgery in this subset of patients.[75] For female patients, indexing LV end-systolic diameter to BSA is already an improvement, compared to the approach recommended in previous guidelines, but even when they are indexed to BSA, women still exhibit smaller ventricular volumes. Hence, a preferable approach is to determine sex-specific thresholds, as the 25 mm/cm^2 that is included in the guidelines is probably too large, and it certainly plays a role in the undertreatment of female patients. Additionally, the regurgitant fraction should be preferred to the effective regurgitant volume area, as it is inherently adapted to a patient's LV size.

Mitral Regurgitation

Prevalence, etiology, and pathophysiology

MR can be subdivided into 2 entities: organic MR and functional MR. Organic MR, also called degenerative or primary MR, results from structural deformity or damage to leaflets, chordae tendineae, or papillary muscles, causing malcoaptation of the mitral leaflets during systole. Consequently, blood flows into the left atrium from the LV during ventricular systole. Common causes include MV prolapse and/or flail, rheumatic disease, papillary muscle rupture, and leaflet perforation.[76] Women present more rheumatic MR, more severe annulus calcification, less flail of leaflets, and more bileaflet or anterior leaflet prolapse MR than do men (Fig. 4).[77-79] Female patients also are known to have more leaflet thickening, which indicates a more generalized myxomatous degeneration than that in male patients.[80]

Functional MR, also called secondary MR, is not caused by a structural problem of the MV, but rather by a LV wall motion abnormality, or LV or LA remodelling, with a dilation of the mitral annulus and displacement of the papillary muscles causing incomplete leaflet coaptation. The prevalence of functional MR is estimated at 2.0-2.5 million people in the US in 2000, and this undoubtedly will increase considerably in upcoming years, as it is expected to reach 4 million in 2030 as the population ages and the rate of postinfarction survival increases.[81,82] Functional MR is one of the most frequent complications of LV remodelling due to coronary artery disease, and it is observed more frequently in male than in female patients.[83] Indeed, in most high-income countries, women develop ischemic heart disease approximately 7 to 10 years later than their male counterparts, with acute coronary syndromes being 3 to 4 times more prevalent in men before age 60 years. However, after the age of 75 years, female sex is associated with a majority of patients presenting with ischemic cardiac events.[84] On the other hand, functional MR as a result of left atrial, and consequently annular, dilatation predominantly affects elderly female patients (58% vs 42% male) with atrial fibrillation.[85]

Diagnosis

Current guidelines provide a recommendation to grade the severity of MR; however, the proposed thresholds are not sex-specific and are not indexed to body size.[16,22] Thus, as women have smaller hearts than men, even for the same body size,[69] current guidelines tend to underestimate the severity of MR in women.[86] As they are less often diagnosed with severe MR and a dilated LV, women's referral to intervention is often delayed,[86-88] and consequently, they present with a worse preoperative profile.[89]

Moreover, elderly women are less active than men of the same age, making them less likely to present with flagrant symptoms. Consequently, physicians may be more likely to refer male patients—who have more-typical cardiac symptoms (ie, chest pain, dyspnea)—to surgery at the appropriate time than women, who exhibit more-subtle symptoms, such as fatigue.[89]

Therapeutic options

If left untreated, severe MR can lead to ventricular dysfunction, left atrial enlargement, secondary atrial fibrillation, and eventually, decompensated heart failure (HF), resulting in a very reserved prognosis.

Organic MR. In patients presenting with severe organic MR, MV surgical repair is the intervention of choice when the valve is deemed repairable. Surgical MV replacement is performed when the valve is deemed unrepairable. If the patient is at prohibitive surgical risk, percutaneous procedures are considered. The literature is clear as to the superiority of surgery over percutaneous intervention, and that of MV repair over replacement, in regard to lower incidence of operative mortality, greater long-term survival, and reduced incidence of reoperation and valve-related complications, in both women and men with severe organic MR.[90]

As women often present with more challenging MV lesions for surgical repair (ie, rheumatic, anterior, or multileaflet prolapse), the crude rate of MV repair is lower in women than it is in men (Fig. 4).[79] However, when evaluated by etiologies, repair is as achievable in women as it is in men, and women derive the same benefit from surgery as men.[86] Rheumatic valve disease in women also is associated with concomitant MV stenosis, which is an indication for valve replacement rather than repair, resulting in worse outcomes.[78,79]

In women, worse outcomes are generally reported after valve surgery for degenerative MR, but this is believed to be a consequence of referral patterns. In fact, male and female patients presenting with the same type and degree of MR, as well as comparable comorbidities, undergo the same types of surgical interventions and exhibit similar outcomes (Fig. 4).[91]

Transcatheter edge-to-edge repair (TEER) is an attractive, minimally invasive option for patients with high surgical risk, as it is deemed to be a safe and effective treatment for both primary and secondary MR. Studies also are being conducted to explore whether the indications for TEER can be widened to include selected patients with moderate surgical risk.[92] Results from the **E**ndovascular **V**alve **E**dge-to-Edge **Re**pair **St**udy (EVEREST II trial) demonstrated the noninferiority of TEER (using a MitraClip) to surgical intervention in patients with severe primary MR, in regard to safety and improvements in clinical outcomes, but it was found to be less effective than surgery at reducing regurgitation.[93]

Functional MR. Regarding functional MR, no consensus has been reached as to the superiority of either valve repair or replacement for treatment when the disease becomes severe and cannot be managed solely pharmacologically.[94] Among patients with symptomatic HF and moderate-to-severe or severe (functional) MR, TEER is associated with better outcomes than medical therapy alone.[95] However, many patients who are at prohibitive risk for surgery are ineligible for transcatheter MV replacement, owing to their having small LV dimensions, severe mitral annulus calcification, and too-small or too-large mitral annular diameters; thus, such patients are treated medically, which generally results in poor outcomes. As small LV dimensions and severe mitral annulus calcification are more frequent in women, more female patients are ineligible for TEER.[96]

Female patients seem to undergo surgical MV repair more often than do male patients, although no difference is seen between the sexes in transcatheter edge-to-edge valve repair frequency. However, women with severe ischemic MR, compared to men, have higher incidence of 2-year mortality, and of major adverse cardiac and cerebrovascular events, and worse 2-year quality of life and functional status after surgical MV repair or replacement.[97]

Prior to MV clip implantation, female patients tend to be older than men, but with fewer comorbidities. All-cause mortality at 1 year, durability of MR reduction, improvement in symptoms, quality of life, and functional quality postintervention are all similar between the 2 groups of patients.[98] Thus, sex should not be considered a critical factor when selecting candidates for TEER or direct annuloplasty, in regard to postintervention outcome.[99,100] However, left atrial enlargement, which is significantly associated with male sex, is a powerful independent predictor of adverse long-term outcome after transcatheter MV repair, for both organic and functional MR.[101,102]

Implications

Addressing bias that affects diagnosis and referral to MV interventions for male vs female patients should be a priority, as early interventions have been proven to improve long-term outcomes in patients with degenerative diseases.[103-105] Furthermore, technical developments in TEER should be a priority, mainly regarding the size of devices, as a high number of surgically inoperable patients who could benefit from such interventions fail screening, because of anatomic features, and are thus treated medically, resulting in higher mortality rates.

Tricuspid Regurgitation

Prevalence, etiology, and pathophysiology

In the US, moderate to severe TR is diagnosed in 0.55% of the general population. The prevalence of TR increases with age, and about 4% of patients aged 75 years or older have clinically significant TR.[106,107] To date, factors predicting TR are not completely understood. Even though men and women share many aspects in regard to the etiology and pathophysiology of heart disease, the literature on the differences in TR between sexes is growing.[108] Furthermore, evidence indicates that female sex is a determinant of TR, and that women are diagnosed with severe TR at a later age, compared to men.[62,109]

TR may be separated into primary and secondary TR, based on etiology, with secondary TR representing about 90% of cases.[106] Primary TR is caused by primitive lesions of the tricuspid valve (TV), and it can be congenital (ie, Ebstein's anomaly, double orifice TV, tricuspid dysplasia, giant right atrium) or acquired (ie, myxomatous degeneration, endocarditis, carcinoid syndrome, rheumatic disease, trauma, and pacemaker- and/or device-related).[110,111] On the other hand, secondary TR is caused by an underlying disease that causes subsequent right ventricular (RV) and/or atrial dilatation, such as left-sided heart disease, pulmonary hypertension, chronic atrial fibrillation, RV dysfunction, and annular dilation. Secondary TR leads to inadequate coaptation between the tricuspid leaflets.[111,112]

TR is rarely isolated and is quite prevalent in association with other VHDs.[113] In addition, multiple studies have noted the higher prevalence of TR in women compared to men in the general population, especially in the community setting, even though this difference may be reduced in the tertiary-care setting.[4,62,106,109] Moreover, the prevalences of etiologies of TR and predisposing factors of TR, including ischemic heart disease, LV dysfunction, left valvular disease, and atrial fibrillation, differs between the sexes.[106,108,114] Among TR patients with no congenital heart disease, nor prior TR surgery, women are more likely to have LV heart disease—related TR and isolated TR etiology. On the other hand, men are more likely than women to have diabetes mellitus, hypercholesterolemia, a smoking habit, coronary artery disease, devices such as an implantable cardioverter-defibrillator (ICD) in situ and pacemaker, larger corrected ventricular size, and worse ventricular dysfunction—related TR.[109]

In terms of pathophysiology, the reason that female sex is associated with a greater burden of disease, more rapid progression, and more symptomatic disease is unclear.[109,115,116] However, the large inherent variability in tricuspid valve anatomy is clear, with varying numbers of leaflets and papillary muscles.[110] A study of the human atrioventricular annuli in postmortem hearts of secondary TR showed that the corrected annular circumference was larger in female patients. On the other hand, male patients

had more myocardium, cellularity, and elasticity in their atrioventricular annuli, which may help them adapt to hemodynamic changes and protect them against annular insufficiency and valvular incompetence. In addition, the larger corrected circumference of the atrioventricular annuli in female patients may limit valvular coaptation.[117] These findings may partly explain why triggers of TR, such as atrial fibrillation, have greater impact on women, in that they cause annular dilatation to a greater extent and a greater predisposition to a higher risk of valvular incompetence.[111,116]

Therapeutic options

Although medical or conservative therapies are available in certain cases, they are very limited (diuretics, aldosterone agonists, pulmonary vasodilators, rhythm control). However, use of medical therapies should not delay an evaluation for surgery or transcatheter-based therapy. In fact, recent work has highlighted the need for early TR intervention to prevent the development of secondary RV damage and severe TR, which is associated with excess mortality and worsening HF.[22,106,118] The treatment of TR also includes both surgical and transcatheter options. However, evidence gaps remain regarding sex-specific considerations for indications and the timing of treatment.[22]

Surgical options

Until recently, surgery was the only definitive treatment for TV disease. However, rates of TR surgery to treat patients with TR disease have been very low, despite isolated TR being associated with excess mortality. In the absence of another indication to undergo cardiac surgery, isolated TR surgery is relatively uncommon. In fact, most severe TR cases have been treated medically.[119] Recently, a strong initiative has advocated for a more proactive surgical approach. The American College of Cardiology guidelines strongly recommend surgical treatment of the TR in patients undergoing left-sided valve surgery. In addition, they recommend surgical treatment in patients with right-sided HF and severe TR, as well as patients with right-sided HF and isolated TR associated with annular dilatation refractory to medical therapy.[16] Surgical repair is the gold standard for secondary TR, and TR annuloplasty has been linked to the best long-term outcome, whereas a surgical replacement is reserved primarily for advanced cases and primary TR.[120] TV surgery of nonsevere TR is, in most cases, not necessary, even in patients undergoing repair of isolated MV prolapse. However, female sex is an independent risk factor for increased TR over time in patients who have undergone MV repair for MR.[121]

Women make up about 60% of those undergoing TV surgery for TR, with the greatest proportion being for cases of TV replacement.[122,123] In addition, women undergoing TV surgery are more likely to have undergone prior valve surgery and to be hypertensive, whereas men are more likely to have coronary disease and chronic kidney disease and to have undergone prior bypass surgery at the time of TV surgery.[122,123] However, no significant sex-specific differences occur in regard to in-hospital mortality, length of hospitalization, or long-term mortality in patients who have undergone isolated TV surgery, although women may have higher rates of redo surgery.[122] An important point to note is that women are known to present with significant TR older than men, as mentioned above, and they have a higher risk of refractory atrial fibrillation or recurrence.[109] Stroke and rheumatic heart disease have been identified as predictors of long-term mortality post−TV replacement and are known to be more common in women. Overall, risk stratification of patients undergoing TV surgery may be important, especially in women, to provide them with the best treatment available.

Transcatheter options

Transcatheter TV interventions (TTVIs) are currently targeted primarily to inoperable or very-high-risk patients with advanced TR,[120] with a 2b level C recommendation for TTVI of severe symptomatic TR in inoperable patients, in European guidelines.[22] Although they are not readily available in the US, 3 feasibility studies have shown that various TTVIs had favourable safety results (ie, low major adverse event rate), improved functional status, were acceptable for low in-hospital mortality, and had significant reduction of the TR and improvement of quality of life.[124-127]

With regard to sex differences, the sex distribution in successful vs unsuccessful TTVI was not statistically significantly different.[127] However, compared to medical treatment, TTVI had a greater decrease in mortality from any cause or rehospitalization for HF in men, compared to women.[127] Additionally, TTVI significantly reduced mortality in the absence of pacemakers and ICDs; however, the difference was inconclusive when patients had pacemakers and/or ICDs. Furthermore, the reduction in mortality and rehospitalization was also fostered by the absence of RV dysfunction estimated visually or by measuring the tricuspid annular plane systolic excursion.[127] An important finding is that LV dysfunction and left valvular disease−related TR had a higher mortality rate, compared to that among patients with primary TR.[109] As mentioned previously, LV dysfunction−related TR is more common in men, whereas left valvular disease−related TR is more frequent in women. Overall, TTVI outcomes may be affected by the sex of the individual, but sex-specific differences are only one of multiple factors affecting the effectiveness and safety of TTVI in the treatment of TR.

Implications

Sex differences have been found in the prevalence, etiology, and pathophysiology of TR disease. In addition, a strong incentive exists for early surgical or transcatheter referral, to improve outcomes, especially for moderate to severe TR disease. Although surgery is still considered the mainstay treatment of TR disease, transcatheter options may provide an interesting alternative. However, significant sex differences exist in the surgical rate, referral latency, surgical redo rate, and outcomes, for both surgical and transcatheter treatments. Standardization of care and risk stratification of patients undergoing TV procedures, as a means to appropriately select the treatment strategy, especially for women, would improve outcomes and reduce inequalities. More research is needed to compare sex differences for the relative performance of surgical and transcatheter-based treatments.

Conclusions

Sex-specific features occur in all major VHDs and have consequences for diagnosis, treatment referral, and treatment choice. Women are more likely to have an underestimated severity of VHD and a delay in treatment referral, owing to a lack of indexing of parameters for severity evaluation and trigger to surgery. Moreover, symptoms are often less pronounced in women and therefore are also underestimated. Sex-specific features of VHDs are also associated with different outcomes after intervention. Thus, to improve women's valvular heart health, these sex-specificities must be accounted for; referral to intervention should not be delayed, and the choice of intervention should be tailored for women.

Ethics Statement

This manuscript does not contain patient data and is therefore not subject to IRB approval.

Patient Consent

The authors confirm that patient consent is not applicable to this article. Patient consent was not needed, as no patient data were used for this article.

Funding Sources

M-A.C. holds the Canada Research Chair on Women's Valvular Heart Health from the Canadian Institutes of Health Research.

Disclosures

M-A.C. received funding from Edwards Lifesciences for computed tomography core laboratory analyses; and research grants from Medtronic and Edwards Lifesciences in the field of surgical aortic valve bioprostheses, with no direct personal compensation.

References

1. Coffey S, Roberts-Thomson R, Brown A, et al. Global epidemiology of valvular heart disease. Nat Rev Cardiol 2021;18:853-64.
2. Watkins DA, Johnson CO, Colquhoun SM, et al. Global, regional, and national burden of rheumatic heart disease, 1990–2015. N Engl J Med 2017;377:713-22.
3. Borer JS, Sharma A. Drug therapy for heart valve diseases. Circulation 2015;132:1038-45.
4. Andell P, Li X, Martinsson A, et al. Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study. Heart 2017;103:1696-703.
5. Clavel MA, Iung B, Pibarot P. A nationwide contemporary epidemiological portrait of valvular heart diseases. Heart 2017;103:1660-2.
6. Frieden P, Blais C, Hamel D, et al. Evolution of the burden of aortic stenosis by sex in the province of Quebec between 2006 and 2018. Heart 2022;108:1644-50.
7. Eveborn GW, Schirmer H, Heggelund G, Lunde P, Rasmussen K. The evolving epidemiology of valvular aortic stenosis. the Tromsø Study. Heart 2013;99:396-400.
8. Côté N, Clavel MA. Sex differences in the pathophysiology, diagnosis, and management of aortic stenosis. Cardiol Clin 2020;38:129-38.
9. Lindman BR, Clavel MA, Mathieu P, et al. Calcific aortic stenosis. Nat Rev Dis Primers 2016;2:16006.
10. Simard L, Côté N, Dagenais F, et al. Sex-related discordance between aortic valve calcification and hemodynamic severity of aortic stenosis. Circ Res 2017;120:681-91.
11. Voisine M, Hervault M, Shen M, et al. Age, sex, and valve phenotype differences in fibro-calcific remodeling of calcified aortic valve. J Am Heart Assoc 2020;9:e015610.
12. Capoulade R, Clavel MA, Le Ven F, et al. Impact of left ventricular remodelling patterns on outcomes in patients with aortic stenosis. Eur Heart J Cardiovasc Imaging 2017;18:1378-87.
13. Dweck MR, Boon NA, Newby DE. Calcific aortic stenosis: a disease of the valve and the myocardium. J Am Coll Cardiol 2012;60:1854-63.
14. Capoulade R, Le Ven F, Clavel MA, et al. Echocardiographic predictors of outcomes in adults with aortic stenosis. Heart 2016;102:934-42.
15. Dahl JS, Eleid MF, Michelena HI, et al. Effect of left ventricular ejection fraction on postoperative outcome in patients with severe aortic stenosis undergoing aortic valve replacement. Circ Cardiovasc Imaging 2015;8:e002917.
16. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease. J Am Coll Cardiol 2021;77:e25-197.
17. Bach DS, Radeva JI, Birnbaum HG, Fournier AA, Tuttle EG. Prevalence, referral patterns, testing, and surgery in aortic valve disease: leaving women and elderly patients behind? J Heart Valve Dis 2007;16:362-9.
18. Bienjonetti-Boudreau D, Fleury MA, Voisine M, et al. Impact of sex on the management and outcome of aortic stenosis patients. Eur Heart J 2021;42:2683-91.
19. Clavel MA, Messika-Zeitoun D, Pibarot P, et al. The complex nature of discordant severe calcified aortic valve disease grading. J Am Coll Cardiol 2013;62:2329-38.
20. Clavel MA, Pibarot P, Messika-Zeitoun D, et al. Impact of aortic valve calcification, as measured by MDCT, on survival in patients with aortic stenosis. J Am Coll Cardiol 2014;64:1202-13.
21. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;143:e35-71.
22. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2022;43:561-632.
23. Shen M, Tastet L, Capoulade R, et al. Effect of age and aortic valve anatomy on calcification and haemodynamic severity of aortic stenosis. Heart 2017;103:32-9.
24. Magne J, Cosyns B, Popescu BA, et al. Distribution and prognostic significance of left ventricular global longitudinal strain in asymptomatic significant aortic stenosis. JACC Cardiovasc Imaging 2019;12:84-92.
25. Shan Y, Pellikka PA. Aortic stenosis in women. Heart 2020;106:970-6.
26. Clavel MA, Malouf J, Michelena HI, et al. B-type natriuretic peptide clinical activation in aortic stenosis. J Am Coll Cardiol 2014;63:2016-25.

27. Henri C, Dulgheru R, Magne J, et al. Impact of serial B-type natriuretic peptide changes for predicting outcome in asymptomatic patients with aortic stenosis. Can J Cardiol 2016;32:183-9.

28. Tribouilloy C, Bohbot Y, Rusinaru D, et al. Excess mortality and undertreatment of women with severe aortic stenosis. J Am Heart Assoc 2021;10:e018816.

29. Hartzell M, Malhotra R, Yared K, et al. Effect of gender on treatment and outcomes in severe aortic stenosis. Am J Cardiol 2011;107:1681-6.

30. Brown JM, O'Brien SM, Wu C, et al. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. J Thorac Cardiovasc Surg 2009;137:82-90.

31. Chaker Z, Badhwar V, Alqahtani F, et al. Sex differences in the utilization and outcomes of surgical aortic valve replacement for severe aortic stenosis. J Am Heart Assoc 2017;6:e006370.

32. Stamou SC, Robich M, Wolf RE, et al. Effects of gender and ethnicity on outcomes after aortic valve replacement. J Thorac Cardiovasc Surg 2012;144:486-92.

33. Elhmidi Y, Piazza N, Mazzitelli D, et al. Sex-related differences in 2197 patients undergoing isolated surgical aortic valve replacement. J Card Surg 2014;29:772-8.

34. Guzzetti E, Poulin A, Annabi MS, et al. Transvalvular flow, sex, and survival after valve replacement surgery in patients with severe aortic stenosis. J Am Coll Cardiol 2020;75:1897-909.

35. Pibarot P, Dumesnil JG. Hemodynamic and clinical impact of prosthesis–patient mismatch in the aortic valve position and its prevention. J Am Coll Cardiol 2000;36:1131-41.

36. Pibarot P, Dumesnil J. Prosthesis-patient mismatch: definition, clinical impact, and prevention. Heart 2006;92:1022-9.

37. Bleiziffer S, Erlebach M, Simonato M, et al. Incidence, predictors and clinical outcomes of residual stenosis after aortic valve-in-valve. Heart 2018;104:828-34.

38. Clavel MA, Webb JG, Pibarot P, et al. Comparison of the hemodynamic performance of percutaneous and surgical bioprostheses for the treatment of severe aortic stenosis. J Am Coll Cardiol 2009;53:1883-91.

39. Pibarot P, Weissman NJ, Stewart WJ, et al. Incidence and sequelae of prosthesis-patient mismatch in transcatheter versus surgical valve replacement in high-risk patients with severe aortic stenosis. J Am Coll Cardiol 2014;64:1323-34.

40. Ternacle J, Pibarot P, Herrmann HC, et al. Prosthesis-patient mismatch after aortic valve replacement in the PARTNER 2 trial and registry. JACC Cardiovasc Interv 2021;14:1466-77.

41. Leone PP, Regazzoli D, Pagnesi M, et al. Implantation of contemporary transcatheter aortic valves in small aortic annuli: the international multicentre TAVI-SMALL 2 registry. EuroIntervention 2023;19:256-66.

42. Herrmann HC, Pibarot P, Hueter I, et al. Predictors of mortality and outcomes of therapy in low-flow severe aortic stenosis. Circulation 2013;127:2316-26.

43. Clavel MA, Berthelot-Richer M, Le Ven F, et al. Impact of classic and paradoxical low flow on survival after aortic valve replacement for severe aortic stenosis. J Am Coll Cardiol 2015;65:645-53.

44. Nombela-Franco L, Rodés-Cabau J, DeLarochellière R, et al. Predictive factors, efficacy, and safety of balloon post-dilation after transcatheter aortic valve implantation with a balloon-expandable valve. JACC Cardiovasc Interv 2012;5:499-512.

45. Unbehaun A, Pasic M, Dreysse S, et al. Transapical aortic valve implantation. J Am Coll Cardiol 2012;59:211-21.

46. Naoum C, Blanke P, Dvir D, et al. Clinical outcomes and imaging findings in women undergoing TAVR. JACC Cardiovasc Imaging 2016;9:483-93.

47. Kodali S, Williams MR, Doshi D, et al. Sex-specific differences at presentation and outcomes among patients undergoing transcatheter aortic valve replacement. Ann Intern Med 2016;164:377.

48. Siontis GCM, Jüni P, Pilgrim T, et al. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR. J Am Coll Cardiol 2014;64:129-40.

49. Ravaux JM, Di Mauro M, Vernooy K, et al. Do women require less permanent pacemaker after transcatheter aortic valve implantation? A meta-analysis and meta-regression. J Am Heart Assoc 2021;10:e019429.

50. Williams M, Kodali SK, Hahn RT, et al. Sex-related differences in outcomes after transcatheter or surgical aortic valve replacement in patients with severe aortic stenosis. J Am Coll Cardiol 2014;63:1522-8.

51. Panoulas VF, Francis DP, Ruparelia N, et al. Female-specific survival advantage from transcatheter aortic valve implantation over surgical aortic valve replacement: meta-analysis of the gender subgroups of randomised controlled trials including 3758 patients. Int J Cardiol 2018;250:66-72.

52. O'Connor SA, Morice MC, Gilard M, et al. Revisiting sex equality with transcatheter aortic valve replacement outcomes. J Am Coll Cardiol 2015;66:221-8.

53. Eltchaninoff H, Bonaros N, Prendergast B, et al. Rationale and design of a prospective, randomized, controlled, multicenter study to evaluate the safety and efficacy of transcatheter heart valve replacement in female patients with severe symptomatic aortic stenosis requiring aortic valve intervention (Randomized researcH in womEn all comers wIth Aortic stenosis [RHEIA] trial). Am Heart J 2020;228:27-35.

54. Malik HT, Sepehripour AH, Shipolini AR, McCormack DJ. Is there a suitable method of anticoagulation in pregnant patients with mechanical prosthetic heart valves? Interact Cardiovasc Thorac Surg 2012;15:484-8.

55. D'Souza R, Ostro J, Shah PS, et al. Anticoagulation for pregnant women with mechanical heart valves: a systematic review and meta-analysis. Eur Heart J 2017;38:1509-16.

56. Simard L, Perron J, Shen M, et al. Vascular burden impact on echocardiographic valvular graft degeneration following a Ross procedure in young adults. J Am Coll Cardiol 2017;70:1099-101.

57. Mazine A, El-Hamamsy I, Verma S, et al. Ross procedure in adults for cardiologists and cardiac surgeons. J Am Coll Cardiol 2018;72:2761-77.

58. Pettersson GB, Blackstone EH. Is it time to reconsider use of the Ross procedure for adults? J Am Coll Cardiol 2018;71:1345-6.

59. Chuang MA, Akodad M, Chatfield A, et al. Frailty assessment of transcatheter aortic valve replacement patients: contemporary practice and future directions. Structural Heart 2021;5:357-66.

60. Afilalo J, Lauck S, Kim DH, et al. Frailty in older adults undergoing aortic valve replacement. J Am Coll Cardiol 2017;70:689-700.

61. Maurer G. Aortic regurgitation. Heart 2006;92:994-1000.

62. Singh JP, Evans JC, Levy D, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol 1999;83:897-902.

63. Ren X, Li F, Wang C, et al. Age- and sex-related aortic valve dysfunction and aortopathy difference in patients with bicuspid aortic valve. Int Heart J 2019;60:637-42.

64. Andrei AC, Yadlapati A, Malaisrie SC, et al. Comparison of outcomes and presentation in men-versus-women with bicuspid aortic valves undergoing aortic valve replacement. Am J Cardiol 2015;116:250-5.

65. Kong WKF, Bax JJ, Michelena HI, Delgado V. Sex differences in bicuspid aortic valve disease. Prog Cardiovasc Dis 2020;63:452-6.

66. Iung B, Baron G, Eric B, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231-43.

67. Goldbarg SH, Halperin JL. Aortic regurgitation: disease progression and management. Nat Clin Pract Cardiovasc Med 2008;5:269-79.

68. Malahfji M, Senapati A, Debs D, et al. Sex differences in myocardial remodeling and extracellular volume in aortic regurgitation. Sci Rep 2023;13:11334.

69. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1-39.e14.

70. Yang LT, Enriquez-Sarano M, Pellikka PA, et al. Sex differences in outcomes of patients with chronic aortic regurgitation: closing the mortality gap. Mayo Clin Proc 2021;96:2145-56.

71. Pfaffenberger S, Bartko P, Graf A, et al. Size matters! Impact of age, sex, height, and weight on the normal heart size. Circ Cardiovasc Imaging 2013;6:1073-9.

72. Jiang J, Liu X, He Y, et al. Transcatheter aortic valve replacement for pure native aortic valve regurgitation: a systematic review. Cardiology 2018;141:132-40.

73. Costanzo P, Bamborough P, Peterson M, et al. Transcatheter aortic valve implantation for severe pure aortic regurgitation with dedicated devices. Interv Cardiol 2022;17:e11.

74. Boon NA, Bloomfield P. The medical management of valvar heart disease. Heart 2002;87:395-400.

75. Thourani VH, Brennan JM, Edelman JJ, et al. Treatment patterns, disparities, and management strategies impact clinical outcomes in patients with symptomatic severe aortic regurgitation. Structural Heart 2021;5:608-18.

76. El Sabbagh A, Reddy YNV, Nishimura RA. Mitral valve regurgitation in the contemporary era. JACC Cardiovasc Imaging 2018;11:628-43.

77. Avierinos JF, Detaint D, Messika-Zeitoun D, Mohty D, Enriquez-Sarano M. Risk, determinants, and outcome implications of progression of mitral regurgitation after diagnosis of mitral valve prolapse in a single community. Am J Cardiol 2008;101:662-7.

78. Vakamudi S, Jellis C, Mick S, et al. Sex differences in the etiology of surgical mitral valve disease. Circulation 2018;138:1749-51.

79. Seeburger J, Eifert S, Pfannmüller B, et al. Gender differences in mitral valve surgery. Thorac Cardiovasc Surg 2012;61:42-6.

80. Avierinos JF, Inamo J, Grigioni F, et al. Sex differences in morphology and outcomes of mitral valve prolapse. Ann Intern Med 2008;149:787.

81. Vajapey R, Kwon D. Guide to functional mitral regurgitation: a contemporary review. Cardiovasc Diagn Ther 2021;11:781-92.

82. Grave C, Tribouilloy C, Tuppin P, et al. Fourteen-year temporal trends in patients hospitalized for mitral regurgitation: the increasing burden of mitral valve prolapse in men. J Clin Med 2022;11:3289.

83. Namazi F, Bijl P, Vo NM, et al. Sex differences in prognosis of significant secondary mitral regurgitation. ESC Heart Fail 2021;8:3539-46.

84. Regitz-Zagrosek V, Oertelt-Prigione S, Prescott E, et al. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. Eur Heart J 2016;37:24-34.

85. Moonen A, Ng MKC, Playford D, et al. Atrial functional mitral regurgitation: prevalence, characteristics and outcomes from the National Echo Database of Australia. Open Heart 2023;10:e002180.

86. Mantovani F, Clavel MA, Michelena HI, et al. Comprehensive imaging in women with organic mitral regurgitation. JACC Cardiovasc Imaging 2016;9:388-96.

87. Kislitsina ON, Zareba KM, Bonow RO, et al. Is mitral valve disease treated differently in men and women? Eur J Prev Cardiol 2019;26:1433-43.

88. LaPar DJ, Likosky DS, Zhang M, et al. Development of a risk prediction model and clinical risk score for isolated tricuspid valve surgery. Ann Thorac Surg 2018;106:129-36.

89. McNeely C, Vassileva C. Mitral valve surgery in women: another target for eradicating sex inequality. Circ Cardiovasc Qual Outcomes 2016;9(2Ssuppl 1):S94-6.

90. Lazam S, Vanoverschelde JL, Tribouilloy C, et al. Twenty-year outcome after mitral repair versus replacement for severe degenerative mitral regurgitation. Circulation 2017;135:410-22.

91. Kandula V, Kislitsina ON, Rigolin VH, et al. Does gender bias affect outcomes in mitral valve surgery for degenerative mitral regurgitation? Interact Cardiovasc Thorac Surg 2021;33:325-32.

92. Layoun H, Harb SC, Krishnaswamy A, et al. Patient selection for mitral transcatheter edge-to-edge repair. Methodist Debakey Cardiovasc J 2023;19:26-36.

93. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med 2011;364:1395-406.

94. Acker MA, Parides MK, Perrault LP, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. N Engl J Med 2014;370:23-32.

95. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med 2018;379:2307-18.

96. Ludwig S, Koell B, Sedighian R, et al. Characteristics and outcomes of patients ineligible for transcatheter mitral valve replacement (TMVR): implications for future device innovation. J Invasive Cardiol 2021;33:E294-301.

97. Giustino G, Overbey J, Taylor D, et al. Sex-based differences in outcomes after mitral valve surgery for severe ischemic mitral regurgitation. JACC Heart Fail 2019;7:481-90.

98. Park SD, Orban M, Karam N, et al. Sex-related clinical characteristics and outcomes of patients undergoing transcatheter edge-to-edge repair for secondary mitral regurgitation. JACC Cardiovasc Interv 2021;14:819-27.

99. Sun F, Liu H, Zhang Q, et al. Sex-specific difference in outcomes after transcatheter mitral valve repair with MitraClip implantation: a systematic review and meta-analysis. J Interv Cardiol 2022;2022:1-8.

100. Werner N, Puls M, Baldus S, et al. Gender-related differences in patients undergoing transcatheter mitral valve interventions in clinical practice: 1-year results from the German TRAMI registry. Catheter Cardiovasc Interv 2020;95:819-29.

101. Iliadis C, Baldus S, Kalbacher D, et al. Impact of left atrial diameter on outcome in patients undergoing edge-to-edge mitral valve repair: results from the German TRAnscatheter Mitral valve Interventions (TRAMI) registry. Eur J Heart Fail 2020;22:1202-10.

102. Balachandran P, Schaff HV, Lahr BD, et al. Preoperative left atrial volume index is associated with postoperative outcomes in mitral valve repair for chronic mitral regurgitation. J Thorac Cardiovasc Surg 2020;160:661-672.e5.

103. Kang DH, Kim JH, Rim JH, et al. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation. Circulation 2009;119:797-804.

104. Suri RM, Vanoverschelde JL, Grigioni F, et al. Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets. JAMA 2013;310:609.

105. Enriquez-Sarano M, Suri RM, Clavel MA, et al. Is there an outcome penalty linked to guideline-based indications for valvular surgery? Early and long-term analysis of patients with organic mitral regurgitation. J Thorac Cardiovasc Surg 2015;150:50-8.

106. Topilsky Y, Maltais S, Medina Inojosa J, et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. JACC Cardiovasc Imaging 2019;12:433-42.

107. Praz F, Muraru D, Kreidel F, et al. Transcatheter treatment for tricuspid valve disease. EuroIntervention 2021;17:791-808.

108. Westerman S, Wenger NK. Women and heart disease, the underrecognized burden: sex differences, biases, and unmet clinical and research challenges. Clin Sci (Lond) 2016;130:551-63.

109. Dietz MF, Prihadi EA, van der Bijl P, et al. Sex-specific differences in etiology and prognosis in patients with significant tricuspid regurgitation. Am J Cardiol 2021;147:109-15.

110. Dahou A, Levin D, Reisman M, Hahn RT. Anatomy and physiology of the tricuspid valve. JACC Cardiovasc Imaging 2019;12:458-68.

111. DesJardin JT, Chikwe J, Hahn RT, Hung JW, Delling FN. Sex differences and similarities in valvular heart disease. Circ Res 2022;130:455-73.

112. Arsalan M, Walther T, Smith RL, Grayburn PA. Tricuspid regurgitation diagnosis and treatment. Eur Heart J 2017;38:634-8.

113. Jaffer S, Foulds HJA, Parry M, et al. The Canadian Women's Heart Health Alliance ATLAS on the epidemiology, diagnosis, and management of cardiovascular disease in women—Chapter 2: scope of the problem. CJC Open 2021;3:1-11.

114. Santoro C, Marco del Castillo A, González-Gómez A, et al. Mid-term outcome of severe tricuspid regurgitation: Are there any differences according to mechanism and severity? Eur Heart J Cardiovasc Imaging 2019;20:1035-42.

115. Prihadi EA, van der Bijl P, Gursoy E, et al. Development of significant tricuspid regurgitation over time and prognostic implications: new insights into natural history. Eur Heart J 2018;39:3574-81.

116. Gual-Capllonch F, Cediel G, Ferrer E, et al. Sex-related differences in the mechanism of functional tricuspid regurgitation. Heart Lung Circ 2021;30:e16-22.

117. El-Busaid H, Hassan S, Odula P, Ogeng'o J, Ndung'u B. Sex variations in the structure of human atrioventricular annuli. Folia Morphol (Warsz) 2012;71:23-7.

118. Chorin E, Rozenbaum Z, Topilsky Y, et al. Tricuspid regurgitation and long-term clinical outcomes. Eur Heart J Cardiovasc Imaging 2020;21:157-65.

119. Kolte D, Elmariah S. Current state of transcatheter tricuspid valve repair. Cardiovasc Diagn Ther 2020;10:89-97.

120. El-Eshmawi A, Pandis D, Adams DH, Tang GH. Tricuspid valve surgery: repair and replacement. Minerva Cardioangiol 2018;66:700-12.

121. Yilmaz O, Suri RM, Dearani JA, et al. Functional tricuspid regurgitation at the time of mitral valve repair for degenerative leaflet prolapse: the case for a selective approach. J Thorac Cardiovasc Surg 2011;142:608-13.

122. Chandrashekar P, Fender EA, Zack CJ, et al. Sex-stratified analysis of national trends and outcomes in isolated tricuspid valve surgery. Open Heart 2018;5:e000719.

123. Pfannmueller B, Eifert S, Seeburger J, et al. Gender-dependent differences in patients undergoing tricuspid valve surgery. Thorac Cardiovasc Surg 2012;61:37-41.

124. Hahn RT, Kodali S, Fam N, et al. Early multinational experience of transcatheter tricuspid valve replacement for treating severe tricuspid regurgitation. JACC Cardiovasc Interv 2020;13:2482-93.

125. Kodali S, Hahn RT, Eleid MF, et al. Feasibility study of the transcatheter valve repair system for severe tricuspid regurgitation. J Am Coll Cardiol 2021;77:345-56.

126. Nickenig G, Weber M, Lurz P, et al. Transcatheter edge-to-edge repair for reduction of tricuspid regurgitation: 6-month outcomes of the TRILUMINATE single-arm study. Lancet 2019;394:2002-11.

127. Taramasso M, Benfari G, van der Bijl P, et al. Transcatheter versus medical treatment of patients with symptomatic severe tricuspid regurgitation. J Am Coll Cardiol 2019;74:2998-3008.