Invited review

Heart valve disease gender difference in the era of transcatheter treatment

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Abstract
Available data have demonstrated important sex-related differences in patients with valvular heart disease, regarding clinical presentation, treatment, and outcomes. Although the calcific aortic stenosis (AS) is more frequent in men compared to women, the majority of AS patients over 80 years old are women, in whom fibrotic remodeling of aortic valve is typically found. Mitral valve disease is more common in women. However females are under-referred or delayed referrals to treatment, probably due to the absence of sex-based LV dimension values guiding surgical timing. The development of transcatheter devices have revolutionized the treatment of valvular heart disease and increased the interest in this topic.
In this context, the consideration of gender differences in presentation, diagnosis, treatment success, and prognosis is of great importance.
Key words: gender, heart valve, transcatheter treatment, aortic valve, mitral valve, tricuspid valve

Introduction

The majority of valve heart disease (VHD) is diagnosed in patients greater than 65 years old, indeed the incidence of VHD increases with age. VHD may equally affect men and women, but sex specific differences in prevalence of valve disease type are described in literature (1-3). Furthermore available data have demonstrated a different risk profiles in women and men affected by heart valve disease, with a significant impact on treatment outcomes and prognosis (4-5). Recently the development of transcatheter devices offers new treatment options for VHD. In this context, although women have been historically underrepresented in most trials investigating transcatheter treatment, the consideration of gender differences in treatment success, and prognosis is of great importance.

This review is an overview of gender-related differences in patients with VHD, regarding incidence, clinical presentation, treatment, and outcomes in the era of transcatheter treatment.

Aortic valve disease

In developed countries, the more common treated VHD is the aortic valve, with the majority of aortic valve disease represented by aortic stenosis. In these countries calcific degeneration of tricuspid aortic valve represents the more common mechanism of aortic stenosis.

In women aortic valve calcium, even after indexing to body surface area or aortic annulus area, is lower compared to men (6-8). Sex-specific hormonal differences are proposed as possible explanation of more calcified aortic valve stenosis in men, in particular testosterone may be involved in greater calcific deposition in the aortic sinus (9). Instead valvular fibrosis is involved in women with hemodynamically severe aortic stenosis, in which a lower degree of aortic valve calcification is typically found (10).

The intramyocardial fibrosis is also more frequent in women compared to men (Fig. 1).

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Some gender differences are also found in clinical presentation of aortic stenosis. In particular at presentation, women are older and have worse symptom burden, including more exercise dizziness and more advanced New York Heart Association class (11) (Fig. 1).

The aortic regurgitation has more marked sex differences than aortic stenosis and is more common among men (12), probably due to the higher incidence of bicuspid aortic valve in male (male- female sex ratio 2:1) (13) and endocarditis (14) (Fig. 1). Similarly to aortic stenosis, a trend of greater symptomatology has also been found in women with aortic regurgitation compared to men (15) (Fig. 1).

Echocardiographic assessment based on sex specific criteria (stroke volume index, size specific left ventricular dimensions and aortic regurgitation) should be considered in order to avoid an underestimation of the severity of valve disease and undertreatment of female patients (Fig. 1).
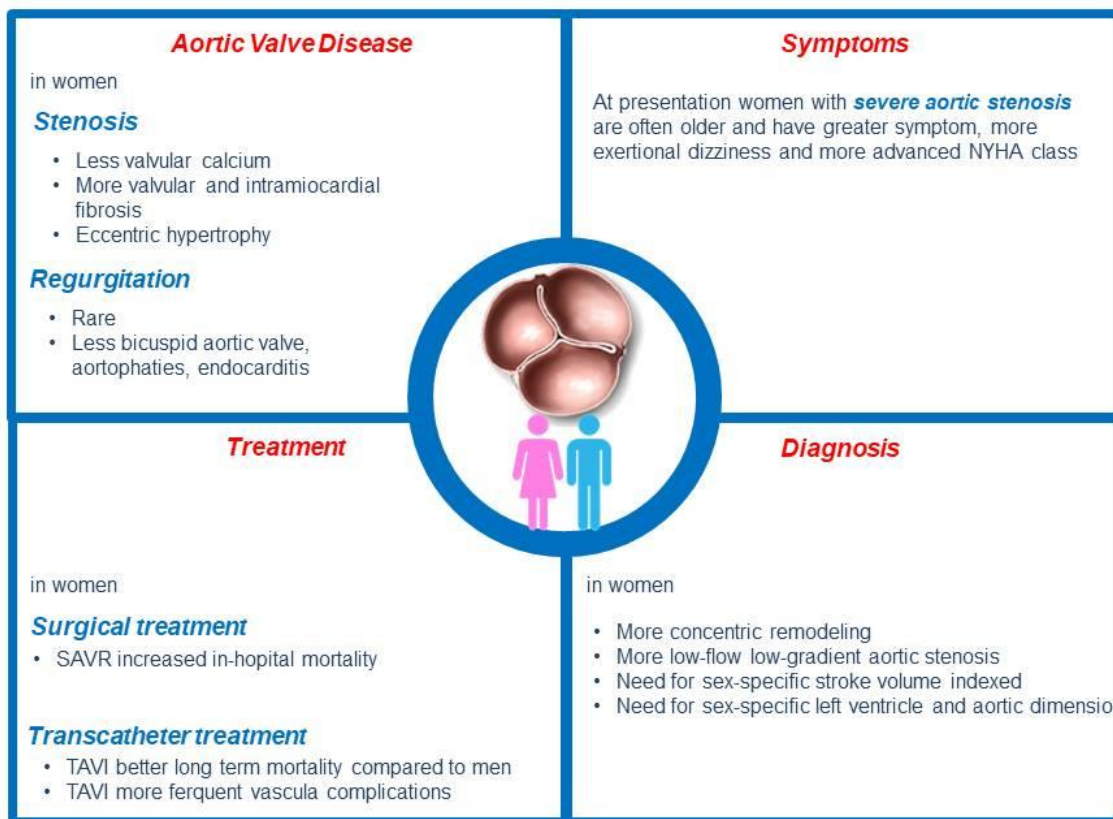

Figure 1. Gender differences in aortic valve disease. Gender-related differences in aortic valve disease regarding incidence, clinical presentation, treatment, and outcomes
SAVR - surgical aortic valve replacement; TAVI - transcatheter aortic valve implantation

Furthermore the fibrotic remodeling of the aortic valve typically of aortic stenosis in women highlights the importance of sex-specific thresholds of aortic valve calcification by cardiac imaging.   Historically the gold standard treatment of aortic stenosis was surgical aortic valve replacement (SAVR).

In the past decade the clinical outcomes of SAVR have improved significantly, but conflicting results on differential sex impact on outcomes are reported by several studies. Data from   Nationwide Inpatient Sample, including 166.809 patients (63% male and 37% female) underwent SAVR between 2003 and 2014 have demonstrated a worse in-hospital mortality following SAVR in women compared to men (5.6% versus 4%, p<0.001). After propensity matching, in-hospital mortality remained significantly higher in women than in men (3.3% versus 2.9%, p=0.001) (16).

The introduction and widespread adoption of transcatheter aortic valve implantation (TAVI) have revolutionized the treatment of aortic stenosis. The clinical outcomes of the 353 women enrolled in the CoreValve US High Risk Pivotal Trial have demonstrated a lower 1-year cardiovascular mortality and a lower 1-year all-cause mortality or major stroke in women undergoing TAVI compared with women undergoing SAVR. Furthermore, as expected, the mean gradient was lower (8.92 (4.17) mmHg vs 12.24 (5.39) mm Hg; p <0.001) and the effective orifice area (EOA) was greater (1.80 (0.53) cm^2 vs 1.44 (0.47) cm^2; p <0.001) in TAVI compared with SAVR. The rate of prosthesis-patient mismatch was lower in female TAVI versus SAVR at 30 days (8.8% vs 29.3%), 6 months (8.1% vs 24.5%), and 1 year (6.9% vs 29.8%) (17).

Several studies have reported superior outcomes with TAVI in women compared with men, partially due to longer life expectancy in women. In SAPIEN 3 Aortic Bioprosthesis European Outcome (SOURCE 3) registry all-cause mortality trended lower in women than men at 4 years post TAVI (18).

An analysis of a contemporary cohort of patients treated with balloon-expandable and self-expandable transcatheter valves found similar rates of in-hospital mortality, stroke, moderate/severe paravalvular leak and pacemaker implantation in women and men (19). Data from Transcatheter Valve Therapy (TVT) registry of the STS/American College of Cardiology (ACC), including 11.808 (49.9%) women and 11.844 (51.1%) men underwent TAVI from 2011-2014 have demonstrated a different risk profile between woman and men and 1-year adjusted survival was superior in female patients, notwithstanding a greater adjusted risk for in-hospital vascular complications (20). Indeed, in TAVI procedure major vascular complications are experienced more frequent in women, probably related to low body surface area and smaller peripheral vessels (21). In WIN TAVI (Women's International Transcatheter Aortic Valve Implantation), an international, multicenter, prospective observational registry of 1019 female patients undergoing TAVI, the Valve Academic Research Consortium 2 (VARC-2) early safety end point (composite of mortality, stroke, major vascular complications, life-threatening bleeding, stage 2 or 3 acute kidney injury, coronary artery obstruction, or repeat procedure for valve-related dysfunction) is reported in 14% and it is manly driven by vascular complications (7.7%) (22) (Fig. 1).

Further information will come from the ongoing Randomized Research in Women All Comers With Aortic Stenosis (RHEIA) trial, a prospective, randomized multicenter study that tests non inferiority and, eventually, the superiority of TAVI versus surgical aortic valve replacement in women with severe aortic stenosis (NCT04160130) (23).

Mitral valve disease

Mitral valve disease represents a quarter of valve heart disease in the developed countries, with mitral regurgitation more common than mitral stenosis. Globally the most common valve disease is the mitral regurgitation, which affected 1-2% of world's population. Rheumatic and non-rheumatic degenerative mitral valve disease is also more common in women compared to men (24). Furthermore women are predisposed to bileaflet mitral valve prolapse, due to more myxomatous valve related to sex-based differences in extracellular matrix remodeling. The posterior mitral valve prolapse with flail is more common in men. Due to these valve morphology differences women with mitral valve prolapse have less frequently severe mitral valve regurgitation (25). Conversely, secondary mitral regurgitation, as a consequence of myocardial infarction or coronary artery disease, occurred more frequent in women compared to men (26).

Gender difference have also been reported in the pathophysiology of mitral apparatus calcification, with posterior leaflet calcification more common in men and mitral annular calcification in women (27) (Fig. 2). Available data have demonstrated gender difference in clinical presentation of mitral valve disease. Postcapillary pulmonary hypertension as expression of adverse pulmonary vascular remodeling is more common in women affected by mitral stenosis (28). Although less dilated ventricles and less severe mitral regurgitation worse heart failure symptoms are more common in women with mitral regurgitation (29) (Fig. 2).

The assessment of the mitral valve anatomy, function and mechanism of abnormalities are performed by echocardiography. Sex and sizes specific parameters should be considered to evaluate left ventricle dilation in the setting of mitral regurgitation. Transesophageal echocardiography is used in pre-procedure assessment and guidance of percutaneous procedures including both repair and replacement (Fig.2).
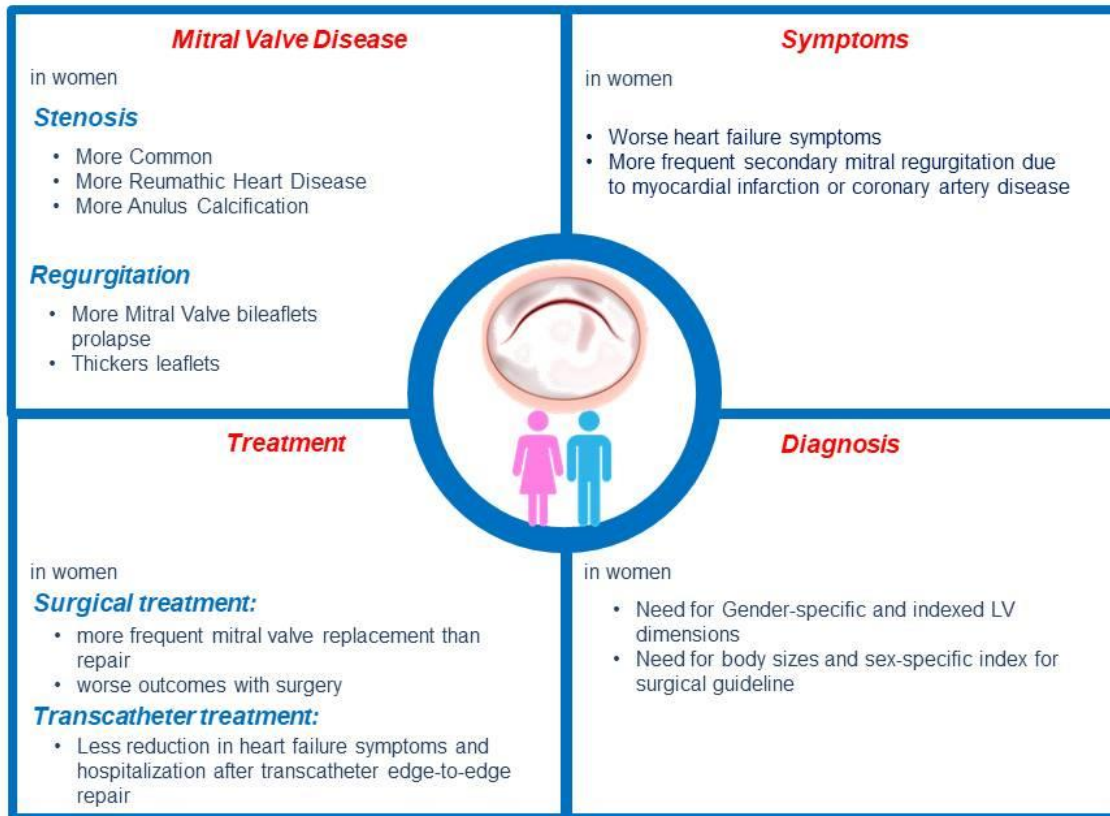
Figure 2. Gender differences in mitral valve disease. Gender-related differences in mitral valve disease regarding incidence, clinical presentation, treatment, and outcomes

Although mitral valve (MV) disease is more common in women compared to men, women are referred for mitral valve intervention at fewer rates and later in the disease course (30). The delayed referral, probably due to cut-off values based primarily on a predominantly male population without sex-based differences, partially explains the worse clinical outcomes after mitral surgery in women (31).

Furthermore in women undergoing surgery for primary or degenerative mitral regurgitation, mitral repair was less performed. Indeed in women MV replacement is performed more frequently compared to men (32). Since MV repair is preferred to replacement for early and late better clinical survival (33), the mortality after MV surgery is higher in women compared to men (32). These differences in intervention and outcomes may be related to frailty, differences in the prevalence and severity of secondary mitral regurgitation, rheumatic valve disease, and mitral annular calcification. Indeed in a propensity score-matched analysis of 846 patients the

surgical approaches for men and women were similar and mortality was comparable (34). These results underlines that the clinical outcomes are dependent upon the later referral, the severity of the mitral disease and associated co-morbidities at the time of surgery (Figure 2).

Rheumatic mitral stenosis is more frequent in women, and data on outcomes after percutaneous balloon mitral valvuloplasty are mixed and it is unclear if there are sex-based differences in outcomes after balloon valvuloplasty (35).

The incident mitral annulus calcification is more frequent in women, therefore in Mitral Annulus Calcification Global Registry 68% of patients were women (36).

Data on percutaneous valve replacement in mitral annulus calcification have demonstrated a worse clinical outcome compared to valve-in-valve and valve-in-ring procedures (37). After transcatheter edge-to-edge repair (TEER) reverse left ventricle remodeling is revealed more frequent in female gender (38).

Nonetheless, the clinical improvements in women treated with TEER seem to be no better compared to men. Indeed studies investigated sex difference in clinical outcomes after TEER have reported contrasting results. The Transcatheter Mitral Valve Interventions (TRAMI) registry (39) and the Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation in Italy (GRASP) registry (40) have reported less improvement in New York Heart Association Class in women compared to men, while the European Registry of Transcatheter Repair for Secondary Mitral Regurgitation (EuroSMR) study have shown equivalent quality of life and symptomatic improvements in both women and men (41).

Women represented only 36% of patients in Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial (42) and only 25% of patients in the Percutaneous Repair With the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR trial) trial (43); this underrepresentation raises questions about the applicability of results to women. In a sex- specific outcomes subanalysis of the COAPT TEER resulted in improved clinical outcomes compared with guideline-directed medical therapy alone, irrespective of sex. However, the reduction in heart failure hospitalizations was less pronounced in women compared to men beyond the first year after treatment (44). Instead data from the Society of Thoracic Surgery/ACC Transcatheter Valve Therapy registry (5.295 patients, 47.6% women enrolled from 2011 to 2017), have demonstrated sex differences in outcomes after TEER, with female sex associated with lower adjusted 1-year risk of all- cause mortality (45). Similarly a meta-analysis of eleven studies with a total of 24.905 patients (45.6% women) have reported that female sex is associated to lower adjusted mortality on long-term follow-up (46).

Further studies are need to confirm sex differences in outcomes after transcatheter edge-to-edge repair (Fig. 2).

Tricuspid valve
According to etiology and mechanism, tricuspid regurgitation (TR) is classified in primary and secondary (47). Primary TR is less common and it is due to congenital and genetic anomalies (Ebstein's anomaly, tricuspid dysplasia, and myxomatous degeneration leading to tricuspid valve prolapse) or due to acquired valve disease (endocarditis, carcinoid, rheumatic involvement). In primary TR the dominant mechanism is tricuspid leaflet abnormalities with variable leaflets mobility and dilatation of tricuspid annulus, right ventricle and right atrium.

Secondary TR represents 90% of all TR and it is characterized by normal valve leaflets with incomplete leaflet coaptation. There are two types of secondary TR: atrial and ventricular. Atrial TR is due to atrial fibrillation/flutter or heart failure with preserved ejection fraction. In atrial TR the dominant mechanism is marked tricuspid valve annulus dilatation; right atrium is also dilated, while leaflets mobility and right ventricle volume are typically normal. Ventricular TR is related to left-sided ventricular or valve disease, pulmonary hypertension, right ventricular cardiomyopathy or infarction. In ventricular regurgitation the dominant mechanism is marked leaflet tethering, with leaflet mobility reduction in systole and dilatation of right annulus, right ventricle and right atrium.

The Framingham Heart Study (48) and other community-based cross sectional studies (49) have demonstrated a female preponderance for mild or severe TR dominance with a male-to-female ratio of 1 to 1.6. Post mortem studies have revealed sex-differences in annular anatomy, with more elastic, more cellular and smaller when correcting for heart weight right atrioventricular annuli in men compared to women (50) (Fig. 3). Consequently, triggers such as atrial fibrillation may cause more frequently annular dilation and secondary TR in women. The progression from moderate to severe TR is also more rapid in women compared to men (51). Furthermore women with secondary TR are older and more symptomatic than men (52) (Fig. 3).
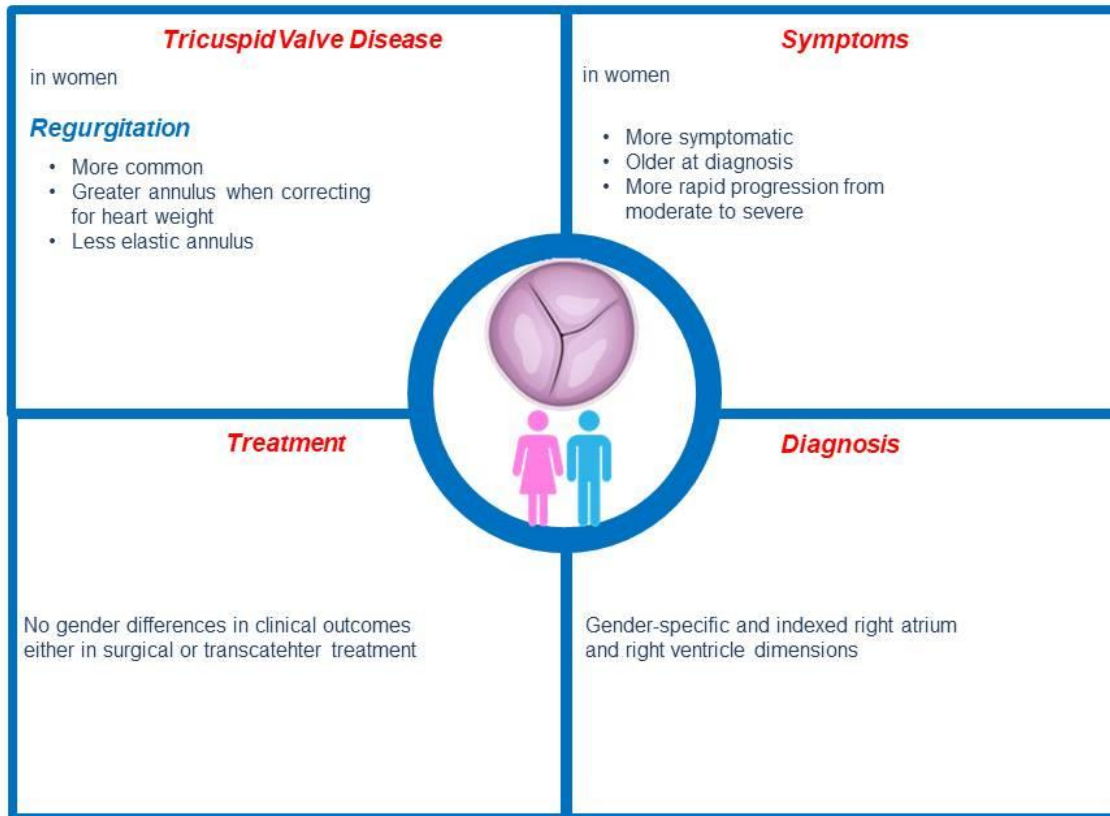
Figure 3. Gender differences in tricuspid valve disease. Gender-related differences in tricuspid valve disease regarding incidence, clinical presentation, treatment, and outcomes

Surgical intervention for isolated TR is a rare intervention with higher in-hospital mortality (8.8%), repair is associated to better clinical outcome compared to replacement (53). In the analysis of data from the National Inpatient Sample women represent the majority of patients undergoing tricuspid surgery and no gender difference is identified in clinical outcomes (54).

Recently different percutaneous treatments for tricuspid regurgitation are proposed. Multiple technologies for transcatheter tricuspid valve repair are available, including coaptation or annuloplasty devices. Data of safety and feasibility trials on these devices reported promising results (55, 56).

Other current transcatheter treatment options include heterotopic caval valve implantation and not yet commercially available transcatheter tricuspid valve replacement with orthotopic valve implantation. The Transcatheter Tricuspid Valve Therapies (TriValve) registry have enrolled patients with severe tricuspid regurgitation undergoing transcatheter tricuspid valve intervention (percutaneous edge-to-edge, annuloplasty, tricuspid replacement) from 2016 to 2021 in 24 centers (57). Data from this registry have demonstrated no difference between men and women in survival, heart failure hospitalization, functional status, and tricuspid regurgitation reduction up to 1 year, but transcatheter tricuspid valve intervention is associated by survival benefit compared to medical therapy alone in both women and men (Fig. 3).
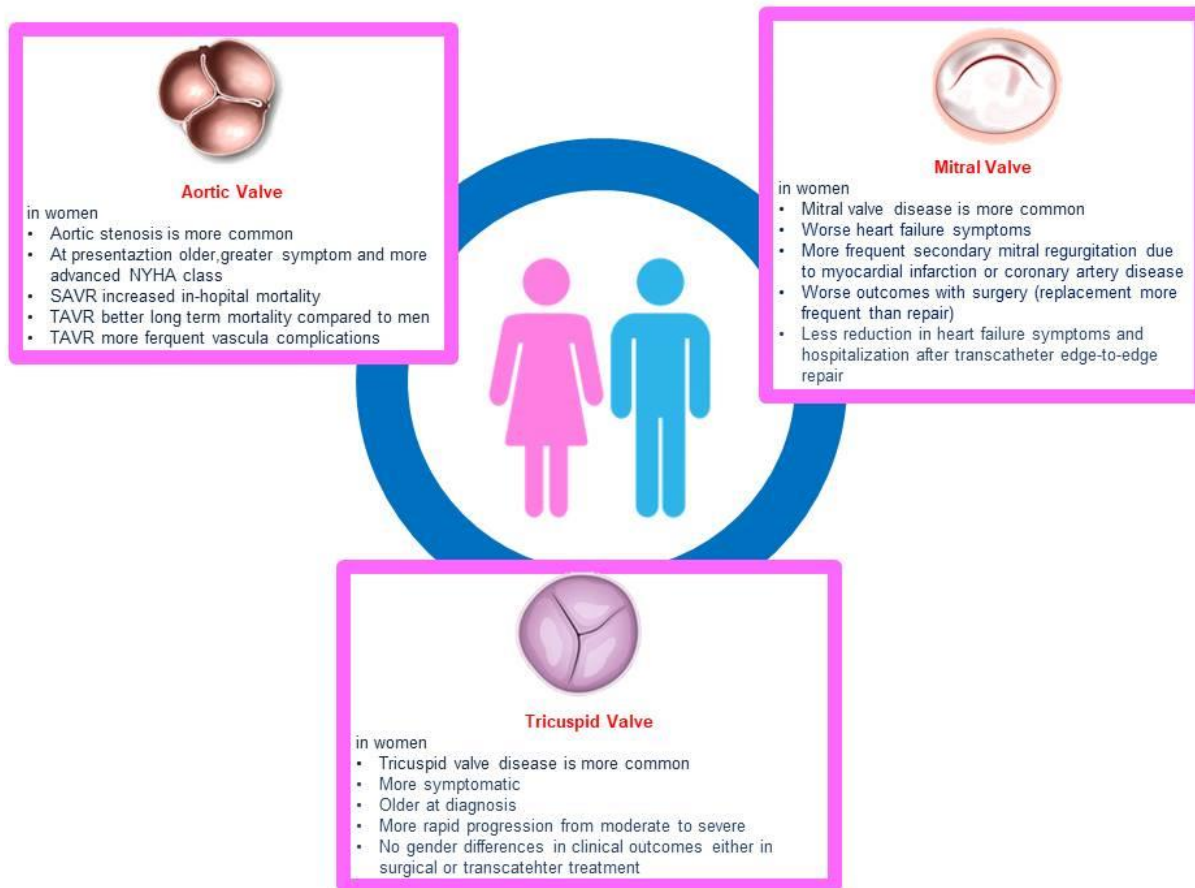
Figure 4. Gender-related differences in heart valve disease

Conclusions

VHD increases significantly among aging populations and important sex-related differences in clinical presentation, treatment, and outcomes are revealed by several studies. A specific risk profile is identified in females with consequently unique challenges for the invasive treatment of the diseased valve (Fig. 4). Implementation of sex-specific treatment criteria should be encouraged in order to guarantee timely referral to treatment.

Future research studies on sex-related differences are need for a tailored management with respect to the timing of intervention and treatment modality to benefit both sexes.

References

1. d'Arcy JL, Coffey S, Loudon MA, Kennedy A, Pearson-Stuttard J, Birks J, et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE Population Cohort Study. Eur Heart J 2016; 37: 3515–22. doi: 10.1093/eurheartj/ehw229

2. Coffey S, Roberts-Thomson R, Brown A, Carapetis J, Chen M, Enriquez-Sarano M, et al. Global epidemiology of valvular heart disease. Nat Rev Cardiol 2021; 18: 853–64. doi: 10.1038/s41569-021-00570-z

3. Andell P, Li X, Martinsson A, Andersson C, Stagmo M, Zöller B, et al. Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study. Heart 2017; 103: 1696–703. doi: 10.1136/heartjnl-2016-310894

4. Nitsche C, Koschutnik M, Kammerlander A, Hengstenberg C, Mascherbauer J. Gender- specific differences in valvular heart disease. Wien Klin Wochenschr 2020; 132: 61-8. doi: 10.1007/s00508-019-01603-x.

5. DesJardin JT, Chikwe J, Hahn RT, Hung JW, Delling FN. Sex differences and similarities in valvular heart disease. Circ Res 2022; 130: 455-73. doi: 10.1161/CIRCRESAHA.121.31991422

6. Aggarwal SR, Clavel MA, Messika-Zeitoun D, Cueff C, Malouf J, Araoz PA, et al. Sex differences in aortic valve calcification measured by multidetector computed tomography in aortic stenosis. Circ Cardiovasc Imaging 2013; 6: 40–7. doi:10.1161/CIRCIMAGING.112.980052

7. Thaden JJ, Nkomo VT, Suri RM, Maleszewski JJ, Soderberg DJ, Clavel MA, et al. Sex-related differences in calcific aortic stenosis: correlating clinical and echocardiographic characteristics and computed tomography aortic valve calcium score to excised aortic valve weight. Eur Heart J 2016; 37: 693–9. doi: 10.1093/eurheartj/ehv560

8. Clavel MA, Messika-Zeitoun D, Pibarot P, Aggarwal SR, Malouf J, Araoz PA, et al. The complex nature of discordant severe calcified aortic valve disease grading: new insights from combined Doppler echocardiographic and computed tomographic study. J Am Coll Cardiol 2013; 62: 2329– 38. doi: 10.1016/j.jacc.2013.08.1621

9. McRobb L, Handelsman DJ, Heather AK. Androgen-induced progression of arterial calcification in apolipoprotein E-null mice is uncoupled from plaque growth and lipid levels. Endocrinology 2009; 150: 841–8. doi:10.1210/en.2008-0760   10. Simard L, Côté N,

Dagenais F, Mathieu P, Couture C, Trahan S, et al. Sex-related discordance between aortic valve calcification and hemodynamic severity of aortic stenosis: is valvular fibrosis the explanation? Circ Res 2017; 120: 681–91. doi: 10.1161/CIRCRESAHA.116.309306

11. Fuchs C, Mascherbauer J, Rosenhek R, Pernicka E, Klaar U, Scholten C, et al. Gender differences in clinical presentation and surgical outcome of aortic stenosis. Heart 2010; 96: 539–45. doi: 10.1136/hrt.2009.186650

12. Andell P, Li X, Martinsson A, Andersson C, Stagmo M, Zöller B, et al. Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study. Heart 2017; 103: 1696–703. doi: 10.1136/heartjnl-2016-310894

13. Sillesen AS, Vøgg O, Pihl C, Raja AA, Sundberg K, Vedel C, et al. Prevalence of Bicuspid aortic valve and associated Aortopathy in newborns in Copenhagen, Denmark. JAMA 2021; 325: 561–567. doi: 10.1001/jama.2020.27205

14. Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol 1999; 83: 897–902. doi: 10.1016/s0002- 9149(98)01064-9

15. Klodas E, Enriquez-Sarano M, Tajik AJ, Mullany CJ, Bailey KR, Seward JB. Optimizing timing of surgical correction in patients with severe aortic regurgitation: role of symptoms. J Am Coll Cardiol 1997; 30: 746–52. doi: 10.1016/s0735-1097(97)00205-2

16. Chaker Z, Badhwar V, Alqahtani F, Aljohani S, Zack CJ, Holmes DR, 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. doi: 10.1161/JAHA.117.006370

17. Skelding KA, Yakubov SJ, Kleiman NS, Reardon MJ, Adams DH, Huang J, et al. Transcatheter aortic valve replacement versus surgery in women at high risk for surgical aortic valve replacement (from the CoreValve US High Risk Pivotal Trial). Am J Cardiol 2016; 118: 560-6. doi: 10.1016/j.amjcard.2016.05.051.

18. Tarantini G, Baumgartner H, Frank D, Husser O, Bleiziffer S, Rudolph T, et al. Four-year mortality in women and men after transfemoral transcatheter aortic valve implantation using the SAPIEN 3. Catheter Cardiovasc Interv 2021; 97: 876-84. doi: 10.1002/ccd.29257.

19. Wang TY, Gracia E, Callahan S, Bilfinger T, Tannous H, Pyo R, et al. Gender disparities in management and outcomes following transcatheter aortic valve implantation with newer generation transcatheter valves. Am J Cardiol 2019; 123: 1489–93.

20. Chandrasekhar J, Dangas G, Yu J, Vemulapalli S, Suchindran S, Vora AN, et al.; STS/ACC TVT Registry. Sex-based differences in outcomes with transcatheter aortic valve therapy: TVT Registry From 2011 to 2014. J Am Coll Cardiol 2016; 68: 2733-44. doi: 10.1016/j.jacc.2016.10.041

21. Szerlip M, Gualano S, Holper E, Squiers JJ, White JM, Doshi D, et al. Sex-specific outcomes of transcatheter aortic valve replacement with the sapien 3 valve: insights from the PARTNER II S3 high-risk and intermediate-risk cohorts. JACC Cardiovasc Interv 2018; 11: 13–20.

22. Chieffo A, Petronio AS, Mehilli J, Chandrasekhar J, Sartori S, Lefèvre T, et al. Acute and 30-day outcomes in women after TAVR: results from the WIN-TAVI (Women's INternational Transcatheter Aortic Valve Implantation) Real-World Registry. JACC Cardiovasc Interv 2016; 9: 1589–600.

23. Eltchaninoff H, Bonaros N, Prendergast B, Nietlispach F, Vasa-Nicotera M, Chieffo A, 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.

24. Yadgir S, Johnson CO, Aboyans V, Adebayo OM, Adedoyin RA, Afarideh M, et al; Global Burden of Disease Study 2017 Nonrheumatic Valve Disease Collaborators. Global, regional, and national burden of calcific aortic valve and degenerative mitral valve diseases, 1990-2017. Circulation 2020; 141: 1670–80.

25. Avierinos JF, Inamo J, Grigioni F, Gersh B, Shub C, Enriquez-Sarano M. Sex differences in morphology and outcomes of mitral valve prolapse. Ann Intern Med 2008; 149: 787–95.

26. Fleury MA, Clavel MA. Sex and race differences in the pathophysiology, diagnosis, treatment, and outcomes of valvular heart diseases. Can J Cardiol 2021; 37: 980–91.

27. Elmariah S, Budoff MJ, Delaney JA, Hamirani Y, Eng J, Fuster V, et al. Risk factors associated with the incidence and progression of mitral annulus calcification: the multiethnic study of atherosclerosis. Am Heart J 2013; 166: 904– 12.

28. Hart SA, Krasuski RA, Wang A, Kisslo K, Harrison JK, Bashore TM. Pulmonary hypertension and elevated transpulmonary gradient in patients with mitral stenosis. J Heart Valve Dis 2010; 19: 708–15.

29. Giustino G, Overbey J, Taylor D, Ailawadi G, Kirkwood K, DeRose J, et al. Sex-based differences in outcomes after mitral valve surgery for severe ischemic mitral regurgitation: from the cardiothoracic surgical trials network. JACC Heart Fail 2019; 7: 481–90.

30. Mantovani F, Clavel MA, Michelena HI, Suri RM, Schaff HV, Enriquez-Sarano M. Comprehensive imaging in women with organic mitral regurgitation: implications for clinical outcome. JACC Cardiovasc Imaging 2016; 9: 388–96.

31. McNeely C, Vassileva C. Mitral valve surgery in women: another target for eradicating sex inequality. Circ Cardiovasc Qual Outcomes 2016; 9: S94–S96.

32. Vassileva CM, McNeely C, Mishkel G, Boley T, Markwell S, Hazelrigg S. Gender differences in long-term survival of Medicare beneficiaries undergoing mitral valve operations. Ann Thorac Surg 2013; 96: 1367–73.

33. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021; 143: e72–e227.

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

35. Mutagaywa RK, Wind AM, Kamuhabwa A, Cramer MJ, Chillo P, Chamuleau S. Rheumatic heart disease anno 2020: impacts of gender and migration on epidemiology and management. Eur J Clin Invest 2020; 50: e13374

36. Guerrero M, Urena M, Himbert D, Wang DD, Eleid M, Kodali S, et al. 1-year outcomes of transcatheter mitral valve replacement in patients with severe mitral annular calcification. J Am Coll Cardiol 2018; 71: 1841–53.

37. Yoon SH, Whisenant BK, Bleiziffer S, Delgado V, Dhoble A, Schofer N, Eschenbach L, et al. Outcomes of transcatheter mitral valve replacement for degenerated bioprostheses, failed annuloplasty rings, and mitral annular calcification. Eur Heart J 2019; 40: 441-51.

38.Adamo M, Godino C, Giannini C, Scotti A, Liga R, Curello S, et al. Left ventricular reverse remodelling predicts long-term outcomes in patients with functional mitral regurgitation undergoing MitraClip therapy: results from a multicentre registry. Eur J Heart Fail 2019; 21: 196–204.

39. Werner N, Puls M, Baldus S, Lubos E, Bekeredjian R, Sievert H, et al; German Transcatheter Mitral Valve Intervention (TRAMI) investigators. 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.

40. Attizzani GF, Ohno Y, Capodanno D, Cannata S, Dipasqua F, Immé S, et al. Gender-related clinical and echocardiographic outcomes at 30-day and 12-month follow up after MitraClip implantation in the GRASP registry. Catheter Cardiovasc Interv 2015; 85: 889–97.

41. Park SD, Orban M, Karam N, Lubos E, Kalbacher D, Braun D, et al; EuroSMR Investigators. 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.

42. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, , et al; COAPT Investigators. Transcatheter mitral- valve repair in patients with heart failure. N Engl J Med 2018; 379: 2307–18.

43.Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, et al; MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med 2018; 379: 2297–306.

44. Kosmidou I, Lindenfeld J, Abraham WT, Rinaldi MJ, Kapadia SR, Rajagopal V, Sarembock IJ, Brieke A, Gaba P, Rogers H, et al. Sex-specific outcomes of transcatheter mitral-valve repair and medical therapy for mitral regurgitation in heart failure. JACC Heart Fail 2021; 9: 674–83.

45. Villablanca PA, Vemulapalli S, Stebbins A, Dai D, So CY, Eng MH, et al. Sex-based differences in outcomes with percutaneous transcatheter repair of mitral regurgitation with the MitraClip System: Transcatheter Valve Therapy Registry From 2011 to 2017. Circ Cardiovasc Interv 2021; 14: e009374.

46. Ya'Qoub L, Gad M, Faza NN, Kunkel KJ, Ya'acoub R, Villablanca P, et al. Sex differences in outcomes of transcatheter edge-to-edge repair with MitraClip: A meta-analysis. Catheter Cardiovasc Interv 2022; 99: 1819-28.

47. Praz F, Muraru D, Kreidel F, Lurz P, Hahn RT, Delgado V, et al. Transcatheter treatment for tricuspid valve disease. EuroIntervention 2021; 17: 791-808.

48. Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, et al. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol 1999; 83: 897–902.

49. Topilsky Y, Maltais S, Medina Inojosa J, Oguz D, Michelena H, et al. Burden of tricuspid regurgitation in patients diagnosed in the community setting. JACC Cardiovasc Imaging 2019; 12: 433–42.

50. 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: 23–27.

51. Prihadi EA, van der Bijl P, Gursoy E, Abou R, Mara Vollema E, Hahn RT, et al. Development of significant tricuspid regurgitation over time and prognostic implications: new insights into natural history. Eur Heart J 2018; 39: 3574–81.

52. Dietz MF, Prihadi EA, van der Bijl P, Fortuni F, Marques AI, Ajmone Marsan N, et al. Sex-specific differences in etiology and prognosis in patients with significant Tricuspid regurgitation. Am J Cardiol 2021; 147: 109–15.

53. Alqahtani F, Berzingi CO, Aljohani S, Hijazi M, Al-Hallak A, Alkhouli M. Contemporary trends in the use and outcomes of surgical treatment of tricuspid regurgitation. J Am Heart Assoc 2017; 6: e007597.

54. Zack CJ, Fender EA, Chandrashekar P, Reddy YNV, Bennett CE, Stulak JM, et al. National trends and outcomes in isolated tricuspid valve surgery. J Am Coll Cardiol 2017; 70: 2953–60.

55. Nickenig G, Weber M, Schüler R, Hausleiter J, Nabauer M, von Bardeleben RS, et al. Tricuspid valve repair with the Cardioband system: two-year outcomes of the multicentre, prospective TRI-REPAIR study. EuroIntervention 2021; 16: e1264-71.

56. Nickenig G, Weber M, Lurz P, von Bardeleben RS, Sitges M, Sorajja 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: 2002-2011.

57. Scotti A, Coisne A, Taramasso M, Granada JF, Ludwig S, Rodés-Cabau J et al. Sex-related characteristics and short-term outcomes of patients undergoing transcatheter tricuspid valve intervention for tricuspid regurgitation. Eur Heart J 2022: ehac735.