Int J Cardiovasc Sci. 2023;36:e20210261

REVIEW ARTICLE

Degenerative Aortic Stenosis in Women: Challenges and Perspectives

Maria Cristina Meira Ferreira,[1] Deborah Christina Nercolini,[2] Mayara Viana de Oliveira,[3] Magaly Arrais dos Santos,[4] Fernanda Mangione,[5] Viviana Lemke,[6] Maria Sanali Moura Paiva,[7] Gláucia Maria Moraes Oliveira[8]

Instituto Nacional de Cardiologia,[1] Rio de Janeiro, RJ – Brazil
Universidade Federal do Paraná,[2] Curitiba, PR – Brazil
Hospital Universitário da Universidade Federal do Maranhão,[3] Imperatriz, MA – Brazil
Instituto Dante Pazzanese de Cardiologia,[4] São Paulo, SP – Brazil
Hospital Beneficência Portuguesa de São Paulo,[5] São Paulo, SP – Brazil
Hospital das Nações,[6] Curitiba, PR – Brazil
Hospital Promater,[7] Natal, RN – Brazil
Universidade Federal do Rio de Janeiro,[8] Rio de Janeiro, RJ – Brazil

Abstract

Degenerative aortic stenosis is currently a public health problem. Affecting the elderly population, this pathology has been showing an increasing prevalence as a direct result of the population aging. In this context, women have a greater life expectancy, corresponding to most of the population with degenerative aortic stenosis. Specific characteristics of this pathology in females are present in the diagnosis, pathophysiology, anatomical aspects, imaging and in therapeutic approach. Women present a more severe disease with less valve calcification than men, more concentric ventricular remodeling, higher transvalvular gradients, and less myocardial fibrosis. Less evident symptoms mean that these patients are referred later for surgical or percutaneous therapeutic treatment. The greater comorbidity presented by females and possibly due to the smaller body surface, bring specific aspects that affect the surgery results, leading to higher mortality rates and, more often, the prosthesis-patient mismatch. Percutaneous valve implantation is a good alternative, with better results in females, when compared to surgery, both in the treatment of native valves and in the treatment of a previously implanted bioprosthesis' dysfunction. The challenges encountered for the treatment of aortic stenosis in women and their possible solutions are described in this article, focusing on the observed difference of aortic stenosis in females and their possible solutions.

Keywords

Aortic Valve Stenosis; Heart Valve Implantation; Transcatheter Aortic Valve Replacement; Heart valve prostheses.

Introduction

According to the GBD 2019, the prevalence of calcified aortic valve disease in Brazil has tended to increase to a total of 201.8%, from 7.9 (95% IU 6.3 - 9.6) per 100,000 in 1990 to 23 .7 (95% IU 19.1 - 29) per 100,000 in 2019, with an increase of 218.8% for men and 182.2% for women.

Although age-standardized mortality decreased in this period, crude mortality rates from calcified aortic valve disease increased sharply by 17% (95% IU 2.0 - 38.5) in the elderly (≥70 years), as a reflection of the aging population and prevalent cardiovascular risk factors. In 2019, the mortality rate from calcified aortic valve disease in Brazil was comparable in men (1.6; II95 1.43-1.82) and women (1.6, II95- 1.32-1.96). On the other hand, women had higher proportional mortality rates from aortic stenosis (AS) in Brazil in 2019 (Figure 1). This highlights the changes in the age distribution of the Brazilian population which shows a notably life expectancy increase in women.[1] These facts have made the treatment of aortic stenosis an important public health issue, especially due to its economic impact. Unless the aortic valve replacement is performed soon after symptoms appear, the mortality rate is estimated to be greater than 50% at 2 years in patients with symptomatic AS.[2]

Mailing Address: Gláucia Maria Moraes Oliveira
Universidade Federal do Rio de Janeiro, Pós-Cardio. R. Prof. Rodolpho Paulo Rocco, 255. Postal code: 22793-060. Rio de Janeiro, RJ – Brazil
E-mail: glauciamoraesoliveira@gmail.com

DOI: https://doi.org/10.36660/ijcs.20210261

Manuscript received November 9, 2021; revised manuscript November 24, 2022; accepted February 15, 2023.

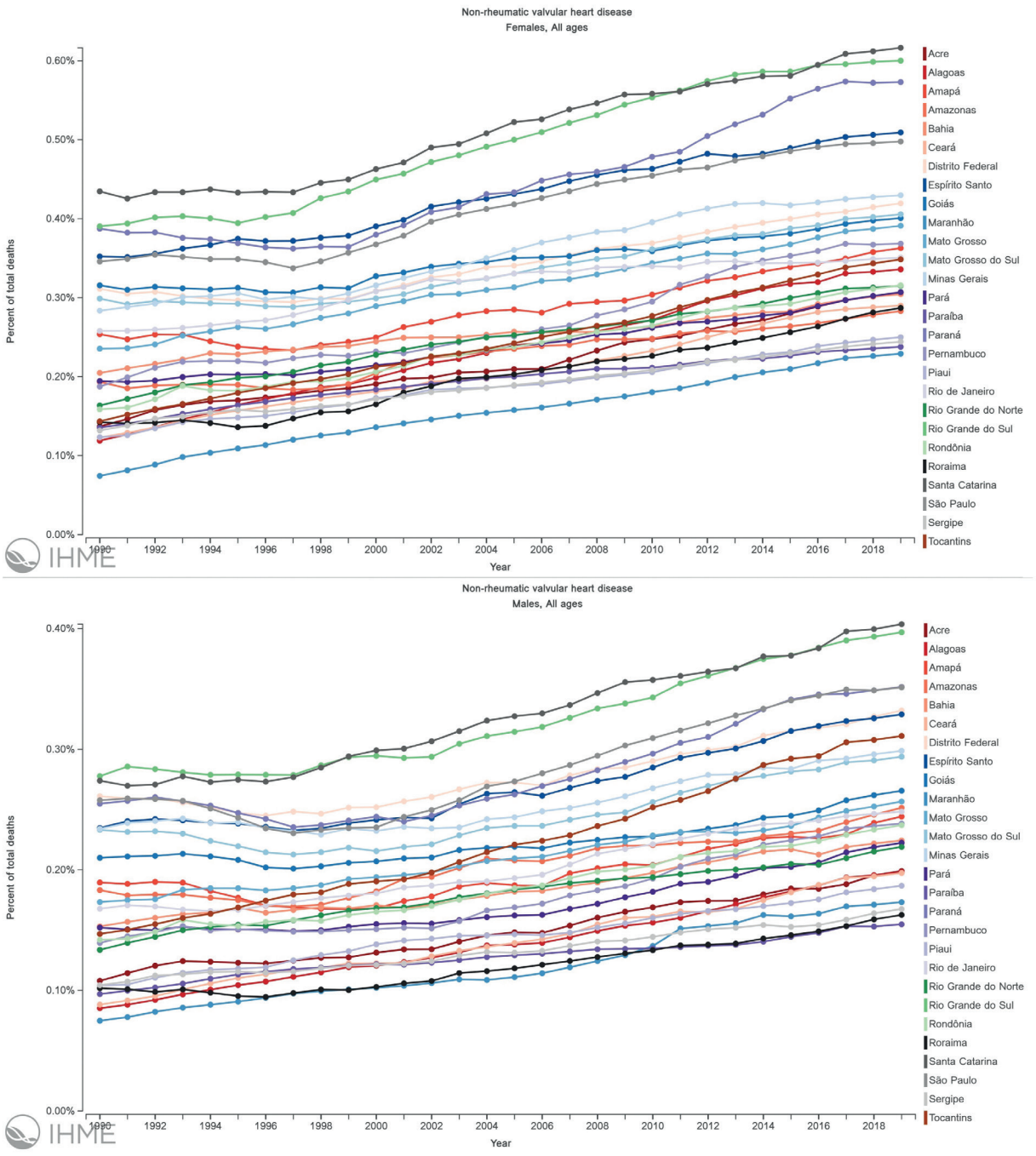

Figure 1 – Proportional mortality rates from non-rheumatic aortic stenosis, both sexes, all ages, Brazil, GBD, from 1990 to 2019, GBD, 2019.

In the treatment of AS, gender-related issues such as dissimilarities in diagnosis, treatment outcomes and prognosis are of great importance.[3] A better understanding of the different forms of development and progression of AS in women is necessary for choosing the therapeutic approach.

Etiopathogenesis of degenerative aortic stenosis

The developmental process of degenerative AS, is an active process, which involves lipids, the renin-angiotensin system, inflammation and genetic predisposition. The scenario begins with stress and

rupture of the basement membrane, subendothelial accumulation of intracellular lipids and lipoproteins, angiogenesis, infiltration of macrophages (foam cells) and T lymphocytes. This inflammatory process allows the activation of native valvular interstitial cells that acquire an osteogenic and procalcific profile and differentiate into osteoblasts. Fibrosis and progressive calcification of the valve leaflets lead to a gradual increase in thickness, stiffness and consequent obstruction of left ventricle (LV) outflow.[3,4]

Clinical factors associated with the progression of the valvular disease are similar to those of coronary atherosclerosis, and LDL-C plays an important role.[4] Advanced age, male gender, hypertension, smoking, diabetes mellitus and metabolic syndrome are common risk factors for both diseases, probably reflecting a common etiopathogenesis. The progression to severe AS is variable between individuals of both sexes.

Valve phenotypes related to clinical presentations

Increasing evidence suggests that gender can determine important distinctions between men and women, in relation to the process of valve calcification, fibrosis and hemodynamic severity of aortic stenosis. These differences lead to implications in the development of different valve phenotypes, left ventricular hypertrophy and cardiovascular outcomes. A recent study showed that, compared to men, women with AS had more pronounced fibrotic remodeling, regardless of valve morphology or patient age.[5]

In addition, higher transvalvular gradients, greater relative wall thickness, and better systolic function were found in women, who often develop more heart failure with preserved ejection fraction (EF), whereas, in general, heart failure when it occurs in men is accompanied often by a reduction in the EF.[6] Transcriptome analysis revealed that a maladaptive left ventricular remodeling may be associated with more pronounced activation of pro-fibrotic and inflammatory markers in men, while fibrosis-related inflammatory pathways are suppressed in women.[7]

Men have higher gene expression of collagen I and III and matrix metalloproteinase (MMP) -2 and -9 in intraoperative biopsies of aortic valve procedures than women, and the levels of collagen I and III are related to the degree of hypertrophy and changes in LV geometry. This may explain the less pronounced interstitial fibrosis in female hearts, as estrogen can prevent the upregulation of collagen, thus inhibiting its synthesis.[8]

The symptoms and progression of patients with AS are determined by the response of the LV to increased afterload, which remodels in order to maintain normal wall tension. Women with severe AS generally show remodeling with more concentric LV geometry, with a greater relative wall thickness, less myocardial fibrosis, and better systolic function compared to men.[8,9] Women are often referred to procedures belatedly due to lower symptomatology and higher life expectancy. In elderly women signs and symptoms are masked by self-limitation resulting from advanced age, often with detection of a drop in ventricular ejection fraction prior to the onset of symptoms, leading to a worse prognosis.[10-12] The inclusion of imaging methods to define severity can help to define the moment of intervention for this gender, since symptoms are less frequently reported and the current indications for an intervention in asymptomatic patients refer to very advanced pathology.

Diagnosis by imaging

Echocardiographic data for the diagnosis and classification of aortic stenosis do not reveal differences between the genders. The echocardiogram, through speckle-tracking echocardiography, can detect incipient ventricular dysfunctions by measuring the global longitudinal strain (GLS), which can help us to define the intervention before the deterioration of ventricular function. Data from a meta-analysis showed that the risk of death for patients with absolute GLS < 14.7% increases by 2.5-fold.[10,13] The measurement of the first-phase ejection fraction (EF-1) on the echocardiogram, which shows the EF obtained in the ejection phase up to the peak of aortic velocity in aortic stenosis, is another factor studied with the purpose of adding prognostic value to AS. The delay in this phase, predicting early impairment of ventricular contractile function, is suggested to have prognostic value, but it needs more data to be used for clinical decision making.[11] A possible echocardiographic interesting point in women is related to the small aortic root more frequent in females that can overestimate the severity of the stenosis due to pressure recovery phenomena.[3,11]

Computed tomography can verify a significant difference in the quantification of the calcium score in the aortic valve between men and women. For the same degree of severity of AS, men have more intense degrees of calcification than women, that is, for the same degree of calcification, women have hemodynamically

more significant stenosis than men. This difference remains even if adjustments are made for a smaller body surface and a smaller valve annulus area in women. The quantification performed by Agatstom, a method that quantifies the intensity of calcium on CT angiography, exhibits a marked interscan, inter and intraobserver reproducibility in this analysis. Data obtained from studies quantify that calcium scores in men ≥ 3000 Agatstom Units (AU), and women ≥ 2000 AU were associated with the very likely presence of severe aortic stenosis, and men ≥ 2000 AU and women ≥ 1600 AU as likely severe AS. This difference in values is directly related to the pathophysiology of AS in women, who have a greater degree of fibrosis and connective tissue deposited in the aortic valves than men, where calcification is more present. When treating the bicuspid aortic valve in women, it is possible to find severe AS with minimal calcification and intense fibrosis.[14,15] The level of valve calcification is the most valuable independent predictor of disease progression in asymptomatic individuals. Aortic calcification density, defined according to gender, has been shown to have similar independent prognostic value for men and women and in all AS subgroups.[16]

Cardiac magnetic resonance imaging (MRI) assists in the assessment of myocardial status in patients with AS by detecting and qualifying the type of myocardial fibrosis by late gadolinium enhancement and by quantifying the extracellular matrix by T1 mapping. The presence of focal fibrosis is considered irreversible even after the correction of the stenosis.[13] Among numerous studies conducted with the objective of early intervention in AS, the Evolved Trial (Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe Aortic Stenosis) is being conducted based on fibrosis image by MRI to assess the prognosis of these patients.[10] Treibel et al., using cardiac MRI, showed differences between the genders in LV remodeling. Normal geometry or concentric remodeling dominated in women, with 82% and 60% of cases respectively. Concentric or eccentric hypertrophy had prevalence higher in men, 71% and 76% respectively. Men more often have myocardial fibrosis with higher focal fibrosis and extracellular expansion. This more adverse pattern in men was related to higher N-terminal portion of B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin T (hsTnT), in addition to greater myocardial fibrosis (focal and diffuse).[9]

Treatment of aortic stenosis

Three large clinical studies, named the Scottish Aortic Stenosis and Lipid Lowering Trial (SALTIRE), the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS), and the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER), failed in an endeavor to prove the benefits of drug treatment in an attempt to delay or prevent the progression of AS, with a consequent decrease in clinical events.[17-19] Drug therapies are useful in relieving symptoms, however, they do not change the clinical progression. In the HAVEC *Registry* patients with severe AS undergoing intervention with EF between 50% and 59% had less favorable outcomes and had more heart failure-related deaths than those with EF > 60% at a 4-year survival observation (63% with EF < 60% x 78% with EF > 60%; $p < 0.05$).[20] Therefore, surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI) are the only treatments capable of modifying the quality of life and the evolutionary prognosis of the pathology.[21,22] The evaluation of the results of SAVR and TAVI showed different aspects between the genders. Analyzing these aspects, would it be possible to infer the existence of a more adequate therapy for women?

Procedures in native aortic valves (SAVR and TAVI)

Surgical Aortic Valve Replacement (SAVR)

The surgery is less performed on women, and when women undergo the surgery, they have an increased mortality rate, with worse long-term results when compared to men.[23-25] Because they are diagnosed later with a more advanced stage of aortic stenosis, they are referred less frequently and belatedly for SAVR, leading to a higher surgical mortality rate.[26]

SAVR can be performed using a conventional approach or a minimally invasive technique using a ministernotomy in the upper third or a minithoracotomy in the second right intercostal space. Despite the aesthetic appeal of the latter for women, there are technical restrictions for the procedure on this gender due to reduced body surface area (BSA) and advanced age.

The choice of prosthesis for aortic valve replacement takes into account the age group, anatomical characteristics, socioeconomic conditions and the patient's consent. The prostheses can be mechanical, biological xenografts (porcine or bovine pericardium), with support or stent (stented prosthesis) or without

support (stentless prosthesis) and biological allografts (cryopreserved human valves).[27,28] In degenerative AS, due to a lower life expectancy and risk of continuous anticoagulation in females, there is a worldwide trend towards the use of biological prostheses.

Specific anatomical aspects of the aortic valve complex in women may explain many of the disparities in treatments for this gender. In a recent sub-analysis of the Simvastatin and Ezetimibe in Aortic Stenosis study, a small root, with a root height <14mm/m in women and <15mm/m in men, was observed in 17% of patients analyzed. These patients had a significantly smaller aortic ring diameter (21.3 mm) when compared to those with a normal aortic root. In this context, there is a strong dominance of females in all studies, accounting for up to 88-91% of patients who receive small prostheses, 19 mm or 21 mm.[29]

A good option for small aortic annulus in females is the use of a stentless bioprosthesis, which have shown better hemodynamic performance when compared to a conventional stented prosthesis, generating smaller aortic transvalvular gradients.[30] However, it has some disadvantages, the technique for implanting stentless is more complex compared to stented; as well as a higher rate of coronary obstruction in patients with a degenerated stentless prosthesis who are subsequently submitted to TAVI using the valve-in-valve (VIV) technique, when compared to stented prosthesis.[31]

Prosthesis-patient mismatch (PPM) is evaluated by measuring the indexed effective orifice area (iEOA), considered insignificant if the iEOA is > 0.85cm²/m², moderate between 0.65 and 0.85cm²/m², and important if <0.65cm²/m².[32] Predictors of PPM are: female gender, advanced age, arterial hypertension, diabetes, renal failure, high body mass index (BMI) and annulus < 23 mm.[32] Due to the higher prevalence of a smaller diameter of the aortic valve annulus (≤ 21 mm); women have a higher risk of PPM.[33-35] To avoid PPM, a larger prosthesis can be implanted using techniques of surgical enlargement of the aortic annulus; however, these are associated with longer surgery and technical difficulty in calcified aortic rings, which may result in increased morbidity.

Aiming to reduce mortality from SAVR in women, alternatives for performing a faster and more effective procedure, with improved hemodynamic functioning and reducing complications, would be a great proposal. Two prostheses aim to achieve this goal. The rapid implant or rapid release prostheses, the Intuity (Edwards Lifescience, Irvine, California, USA), which is fixed in the aortic annulus with only three stitches, and has a stent for fixation in the left ventricular outflow tract. Another alternative is the self-expanding, sutureless nitinol prosthesis, Perceval S (LivaNova, London, United Kingdom), which does not require sutures for fixation to the aortic annulus. Both have some limitation for a bicuspid aorta. The results obtained are favorable, especially in minimally invasive procedures.[36,37] Although we do not yet have comparative data between the genders, these results may alter the disadvantages in the surgery for women.

Transcatheter aortic valve implantation (TAVI)

Women have a longer life expectancy than men, therefore, more degenerative AS, representing a larger portion of patients undergoing TAVI,[38] wich is more frequently indicated because it is a less invasive procedure with good results.[39,40] Although underrepresented in coronary trials, a metanalyses including 11.310 patients refers that women represent almost half of patients evaluated in TAVI studies.[41]

The lower mortality rate for women vs men on TAVI has been reported in several studies, including a recent meta-analysis by Siontis et al.[42] One of the possible factors is the fact that women have lower acute renal failure rates, and another could be the fact that women have a lower risk of moderate/severe aortic insufficiency (AI) after TAVI. Both well-known factors for increased post-procedure mortality. Women received more balloon-expandable prostheses (Sapien - Edwards Lifescience, Irvine, California, USA), while men received more self-expanding prostheses (CoreValve and Evolut - Medtronic, Minneapolis, Minnesota, USA), which may have contributed to less AI in women when compared to men.[43] Another fact was evidenced in the meta-analysis by Saad et al,[43] which involved 17 studies, reporting that the higher number of self-expanding prostheses implanted in men compared to women led to a greater need for a permanent pacemaker in men (17% vs 10, 4%), a factor that also influences the increase in mortality.

The choice of prosthesis depends on the anatomical evaluation through computed tomography. Female patients, due to the smaller diameter of the aortic annulus, may benefit from transcatheter prostheses with a supra-annular attribute, such as the Evolut (Medtronic, Minneapolis, Minnesota, USA), Portico (Abbott, Aboott Park, Illinois, USA) or Accurate (Boston Scientific,

Massachusetts, Massachusetts, USA). Self-expanding prostheses present a better hemodynamic performance than annular balloon expandable protheses, with a lower transvalvular gradient and higher EOA, as well as providing a lower incidence of rupture. Actually there is still no evidence that this finding translates into reduce incidence of adverse outcomes as mortality, rehospitalization or prothesis degeneration.[44] Based on that, the newly launched SMART trial was designed to answer this question [45] Another aspect that is more common in women, a lower-height coronary artery, may also require specific types of prostheses to avoid coronary occlusion. The use of completely repositionable prostheses, such as Evolut and Portico, may have an advantage over other prostheses as they can be repositioned, allowing the procedure to be reversed in case of occlusion.[46] The Accurate prosthesis has technical specifications that accept its use for lower coronary arteries and clinical records show lower numbers of coronary occlusion than other prostheses, but we still do not have comparative randomized studies.[47] Finally, procedures with complex techniques, using coronary protection devices, may prevent occlusion.

Femoral access is always the first choice for TAVI as it leads to the best results. Women have smaller and more tortuous arteries, which can limit transfemoral access.[48] Female patients often undergo TAVI through alternative, non-femoral routes. However, with the technological advances of all prostheses, which have become more flexible and smaller in caliber, making it possible to perform TAVI in arteries of increasingly smaller diameters, there has been a significant reduction in TAVI performed through alternative access routes.[49]

Some complications related to TAVI are mentioned as more frequent in women: major vascular complications, major bleeding, coronary occlusion, rupture of the aortic valve annulus and left ventricular perforation. Vascular complications are almost twice as frequent in women. This is likely due to smaller femoral arteries in comparison to men's and smaller stature.[50] Life-threatening bleeding or severe bleeding has a 50% higher incidence in females than in males. This discrepancy is more pronounced in patients with a lower BMI.[37] In the largest multicenter registry reporting post-TAVI coronary obstruction, the vast majority (>80%) of patients were women.[51] Ring rupture is rare, possibly due to the smaller diameter of the ring in women. In the series reported by Barbanti et al.,[52] 74% of the patients who developed annular rupture were women. Left ventricular perforation is a very rare complication, but more frequent in females, possibly due to the smaller size of this cavity in women.[44]

Although the post-TAVI complications described above occur more frequently in women, this has not interpreted into an increased mortality rate. In a meta-analysis of 27,186 patients, correction of AS in women using TAVI demonstrated significantly lower one-year mortality than SAVR. One of the reasons for this finding would be a lower occurrence of PPM, which would facilitate greater recovery of systolic ventricular function.[53]

Therapeutic procedures in failure of valve prostheses

The degeneration of surgical or percutaneous prostheses and the occurrence of PPM are considered reasons for an intervention. A reoperation (*redo*-surgery) for the replacement of a degenerated bioprosthesis is, to date, considered the gold standard approach for patients with a dysfunctional bioprosthesis. However, when compared to the first surgery, redo-surgery has higher rates of morbidity and mortality. Considering that women already have a higher mortality rate for the first surgery, the limitation of this approach is accentuated.

On the other hand, studies demonstrated the feasibility and safety of the VIV procedure, which consists of the implantation of a transcatheter bioprosthesis inside the dysfunctional surgical bioprosthesis. The medium-term follow-up of these patients showed improvement in hemodynamic status and excellent functional results, and its indication was recently incorporated into North American and European cardiology guidelines.[22,54] In a recent meta-analysis, Mahmoud et al described the results of this procedure in a series of 22 studies, totaling 5,553 patients undergoing VIV.[55] In that review, a 97% success rate was observed, with 5% mortality and 2% stroke within 30 days. In long-term follow-up, a subanalysis of the VIVID registry published by Bleiziffer et al with 1006 VIV procedures performed more than five years ago observed a lower eight-year survival in patients who came in with a failed bioprosthesis with an internal diameter ≤ 20 mm. Independent predictors of mortality included small prostheses, including those with PPM, and non-transfemoral access, both of which were more prevalent in women.[56]

Literature data on PPM are poorly explained due to the difference between PPM measurements in post-surgery and post-TAVI studies. They are different concepts and different measures used. Most post SAVR studies

have used the predicted EOA to define PPM, which is calculated by dividing the normal reference value of EOA for model and prosthesis size by the patient's BMI. TAVI studies do not use the predicted PPM, they have used the iEOA measured by echodopplercardiography to identify PPM, resulting in what is known as measured PPM. In a study published by Ternacle et al,[57] if the predicted EOA measurement after TAVI is used, most patients with PPM will be reclassified to those without PPM after TAVI.

In cases of TAVI prosthesis failure, comparison of the results of implanting a second prosthesis by TAVI inside the dysfunctional (redo-TAVI) vs. VIV in the International Redo-TAVI Registry showed no difference in 30-day and 1-year mortality, and larger area and smaller residual mean gradient were observed in patients undergoing redo-TAVI. The rate of ≥ moderate residual aortic regurgitation (AR) was the same in both groups, but there was a difference in mild AR, which was higher in the redo-TAVI group.[58] These results are encouraging for a future therapeutic alternative, given the greater number of women undergoing TAVI. Concerns about the durability of these transcatheter prostheses can be minimized knowing that the redo-TAVI alternative is comparable to the VIV alternative.

Although we do not have studies looking at VIV outcomes specifically in women, it is important to take into account all aspects of the studies described above that may be beneficially applicable to women.

Two techniques, which require greater expertise, are described to enable transcatheter VIV procedures in more complex anatomies. First, when the implanted surgical bioprosthesis is small, inflating a balloon inside it to break the ring, allowing VIV to be performed with a higher iEOA becomes an alternative. A study of this technique in 75 patients at 25 centers demonstrated that the procedure can be performed safely with a significant reduction in the final residual gradient.[59] A second technique, the procedure called BASILICA (Bioprosthetic or Native Aortic Scallop Intentional Laceration to Prevent Iatrogenic Coronary Artery Obstruction), consists of the intentional laceration of the bioprosthesis leaflet to prevent iatrogenic obstruction of the coronary artery during VIV implantation, and can also be used in a native aortic artery when submitted to TAVI. According to the BASILICA international registry, which included 214 patients from 25 centers in the United States and Europe, leaflet laceration was successful in 94.4% of patients, with partial or complete coronary obstruction in 4.7% of cases.[60]

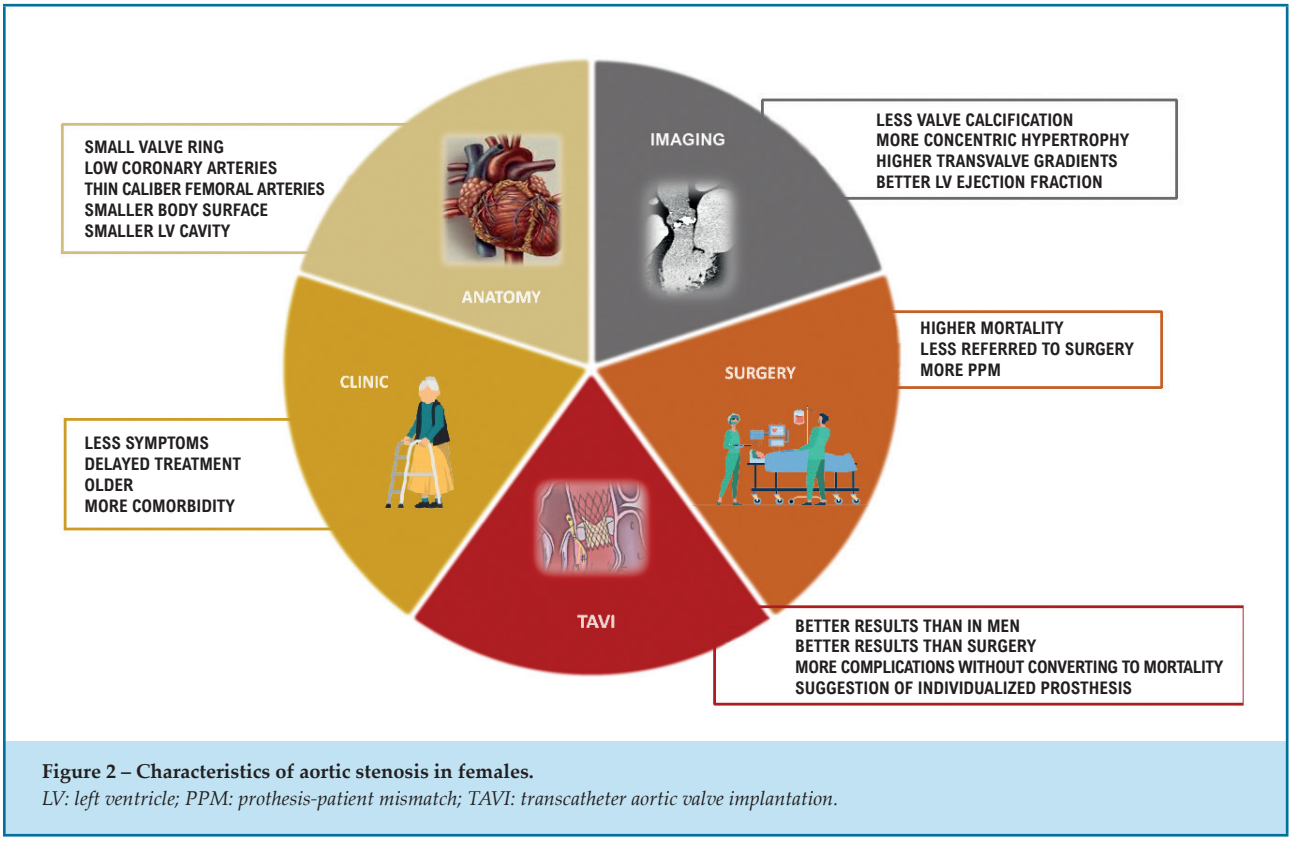

Figure 2 – Characteristics of aortic stenosis in females.
LV: left ventricle; PPM: prothesis-patient mismatch; TAVI: transcatheter aortic valve implantation.

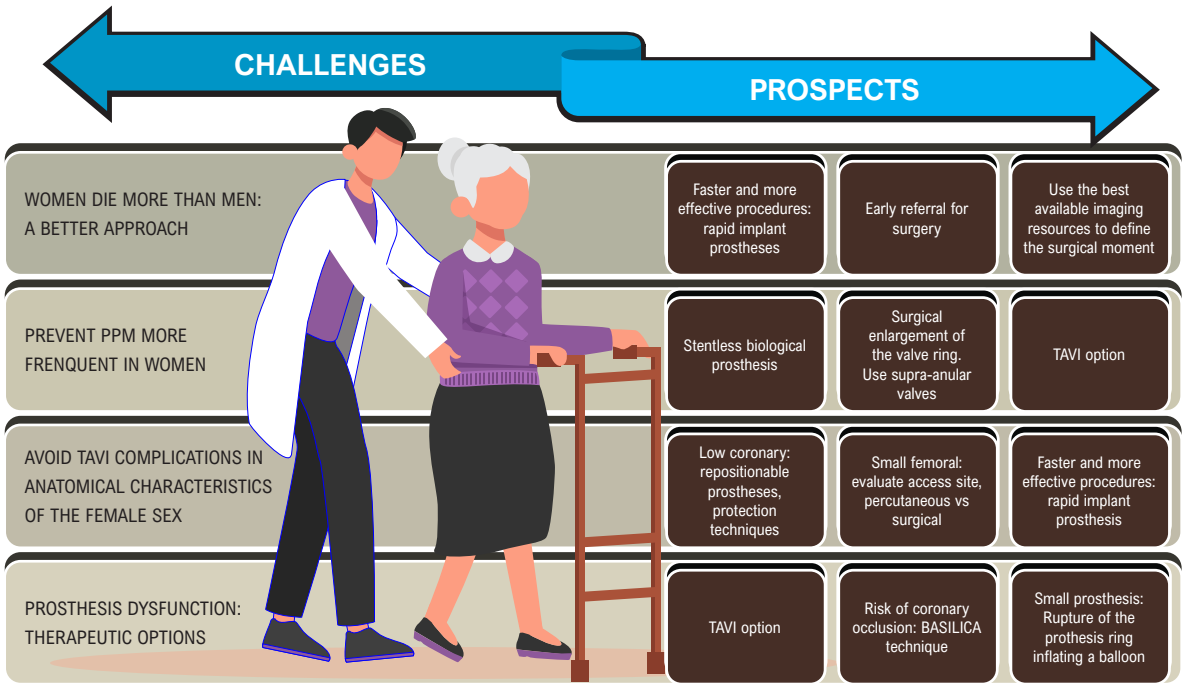

Figure 3 – Challenges in the treatment of women with aortic stenosis and possible solutions.
PPM: prosthesis-patient mismatch; TAVI: transcatheter aortic valve implantation.

Synopsizing the above, figures 2 and 3 are central figures, they represent a general summary of the important aspects contained in different parts of this text. Figure 2 presents the characteristics of degenerative aortic stenosis in women, enumerating anatomical, clinical, pathophysiological and therapeutic aspects present in females. Figure 3 seeks a correlation between the differences found and the prospects for a solution for each challenge that is presented.

Conclusion

In women, severe AS with fibrotic degeneration is more frequently observed than the calcified phenotype, which predominates in men. This suggests that, rather than the typical profibrotic remodeling paradigm that progresses to calcification, female valve disease results from a continuous accumulation of collagen. A smaller symptomatology is observed, possibly due to self-limitation due to advanced age, and there may be a drop in the ventricular ejection fraction before the presentation of symptoms, leading to a worse prognosis due to the delay in the intervention. Several studies have shown that SAVR is associated with a higher risk for women compared to men. The increase in mortality and 30-day SAVR in women is possibly due to increasing age, comorbidities, and higher in-hospital mortality. TAVI, unlike SAVR, has proven benefits in women, with superior results in terms of hospital mortality, as well as in terms of medium and long-term outcomes, when compared to their male counterparts.

Author contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data and writing of the manuscript: Ferreira MCM, Nercolini DC, De Oliveira MV, Dos Santos MA, Mangione F, Paiva MSM, De Oliveira GMM; critical revision of the manuscript for intellectual content: Ferreira MCM, De Oliveira GMM.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Lopes MACQ, Nascimento BR, Oliveira GMM. Treatment of Aortic Stenosis in Elderly Individuals in Brazil: How Long Can We Wait? Arq Bras Cardiol. 2020;114(2):313-8. doi: 10.36660/abc.2020003.
2. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, et al. Two-Year Outcomes after Transcatheter or Surgical Aortic-Valve Replacement. N Engl J Med. 2012;366(18):1686-95. doi: 10.1056/NEJMoa1200384.
3. Summerhill VI, Moschetta D, Orekhov AN, Poggio P, Myasoedova VA. Sex-Specific Features of Calcific Aortic Valve Disease. Int J Mol Sci. 2020;21(16):5620. doi: 10.3390/ijms21165620.
4. Valerio V, Myasoedova VA, Moschetta D, Porro B, Perrucci GL, Cavalca V, et al. Impact of Oxidative Stress and Protein S-Glutathionylation in Aortic Valve Sclerosis Patients with Overt Atherosclerosis. J Clin Med. 2019;8(4):552. doi: 10.3390/jcm8040552.
5. Voisine M, Hervault M, Shen M, Boilard AJ, Filion B, Rosa M, et al. Age, Sex, and Valve Phenotype Differences in Fibro-Calcific Remodeling of Calcified Aortic Valve. J Am Heart Assoc. 2020;9(10):e015610. doi: 10.1161/JAHA.119.015610.
6. Singh A, Chan DCS, Greenwood JP, Dawson DK, Sonecki P, Hogrefe K, et al. Symptom Onset in Aortic Stenosis: Relation to Sex Differences in Left Ventricular Remodeling. JACC Cardiovasc Imaging. 2019;12(1):96-105. doi: 10.1016/j.jcmg.2017.09.019.
7. Kararigas G, Dworatzek E, Petrov G, Summer H, Schulze TM, Baczko I, et al. Sex-Dependent Regulation of Fibrosis and Inflammation in Human Left Ventricular Remodelling Under Pressure Overload. Eur J Heart Fail. 2014;16(11):1160-7. doi: 10.1002/ejhf.171.
8. Petrov G, Regitz-Zagrosek V, Lehmkuhl E, Krabatsch T, Dunkel A, Dandel M, et al. Regression of Myocardial Hypertrophy after Aortic Valve Replacement: Faster in Women? Circulation. 2010;122(11 Suppl):S23-8. doi: 10.1161/CIRCULATIONAHA.109.927764.
9. Treibel TA, Kozor R, Fontana M, Torlasco C, Reant P, Badiani S, et al. Sex Dimorphism in the Myocardial Response to Aortic Stenosis. JACC Cardiovasc Imaging. 2018;11(7):962-73. doi: 10.1016/j.jcmg.2017.08.025.
10. Lindman BR, Dweck MR, Lancellotti P, Généreux P, Piérard LA, O'Gara PT, et al. Management of Asymptomatic Severe Aortic Stenosis: Evolving Concepts in Timing of Valve Replacement. JACC Cardiovasc Imaging. 2020;13(2 Pt 1):481-93. doi: 10.1016/j.jcmg.2019.01.036.
11. Bing R, Dweck MR. Management of Asymptomatic Severe Aortic Stenosis: Check or all in? Heart. 2021;107(10):842-50. doi: 10.1136/heartjnl-2020-317160.
12. Reid A, Blanke P, Bax JJ, Leipsic J. Multimodality Imaging in Valvular Heart Disease: How to Use State-Of-The-Art Technology in Daily Practice. Eur Heart J. 2021;42(19):1912-25. doi: 10.1093/eurheartj/ehaa768.
13. Lancellotti P, Magne J, Dulgheru R, Clavel MA, Donal E, Vannan MA, et al. Outcomes of Patients with Asymptomatic Aortic Stenosis Followed Up in Heart Valve Clinics. JAMA Cardiol. 2018;3(11):1060-8. doi: 10.1001/jamacardio.2018.3152.
14. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease. Eur Heart J. 2017;38(36):2739-91. doi: 10.1093/eurheartj/ehx391.
15. Summerhill VI, Moschetta D, Orekhov AN, Poggio P, Myasoedova VA. Sex-Specific Features of Calcific Aortic Valve Disease. Int J Mol Sci. 2020;21(16):5620. doi: 10.3390/ijms21165620.
16. Utsunomiya H, Yamamoto H, Kitagawa T, Kunita E, Urabe Y, Tsushima H, et al. Incremental Prognostic Value of Cardiac Computed Tomography Angiography in Asymptomatic Aortic Stenosis: Significance of Aortic Valve Calcium Score. Int J Cardiol. 2013;168(6):5205-11. doi: 10.1016/j.ijcard.2013.07.235.
17. Cowell SJ, Newby DE, Prescott RJ, Bloomfield P, Reid J, Northridge DB, et al. A Randomized Trial of Intensive Lipid-Lowering Therapy in Calcific Aortic Stenosis. N Engl J Med. 2005;352(23):2389-97. doi: 10.1056/NEJMoa043876.
18. Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, et al. Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis. N Engl J Med. 2008;359(13):1343-56. doi: 10.1056/NEJMoa0804602.
19. Chan KL, Teo K, Dumesnil JG, Ni A, Tam J; ASTRONOMER Investigators. Effect of Lipid Lowering with Rosuvastatin on Progression of Aortic Stenosis: Results of the Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin (ASTRONOMER) Trial. Circulation. 2010;121(2):306-14. doi: 10.1161/CIRCULATIONAHA.109.900027.
20. Lancellotti P, Magne J, Dulgheru R, Clavel MA, Donal E, Vannan MA, et al. Outcomes of Patients with Asymptomatic Aortic Stenosis Followed Up in Heart Valve Clinics. JAMA Cardiol. 2018;3(11):1060-8. doi: 10.1001/jamacardio.2018.3152.
21. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135(25):e1159-e1195. doi: 10.1161/CIR.0000000000000503.
22. 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: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021;143(5):e35-e71. doi: 10.1161/CIR.0000000000000932.
23. Kontis V, Bennett JE, Mathers CD, Li G, Foreman K, Ezzati M. Future Life Expectancy in 35 Industrialised Countries: Projections with a Bayesian Model Ensemble. Lancet. 2017;389(10076):1323-35. doi: 10.1016/S0140-6736(16)32381-9.
24. 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(4):362-9.
25. 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(9):e006370. doi: 10.1161/JAHA.117.006370.
26. Tribouilloy C, Bohbot Y, Rusinaru D, Belkhir K, Diouf M, Altes A, et al. Excess Mortality and Undertreatment of Women with Severe Aortic Stenosis. J Am Heart Assoc. 2021;10(1):e018816. doi: 10.1161/JAHA.120.018816.
27. Jaffer IH, Whitlock RP. A Mechanical Heart Valve is the Best Choice. Heart Asia. 2016;8(1):62-4. doi: 10.1136/heartasia-2015-010660.
28. Chiang YP, Chikwe J, Moskowitz AJ, Itagaki S, Adams DH, Egorova NN. Survival and Long-Term Outcomes Following Bioprosthetic vs Mechanical Aortic Valve Replacement in Patients Aged 50 to 69 Years. JAMA. 2014;312(13):1323-9. doi: 10.1001/jama.2014.12679.
29. Freitas-Ferraz AB, Tirado-Conte G, Dagenais F, Ruel M, Al-Atassi T, Dumont E, et al. Aortic Stenosis and Small Aortic Annulus. Circulation. 2019;139(23):2685-702. doi: 10.1161/CIRCULATIONAHA.118.038408.

30. van der Straaten EP, Rademakers LM, van Straten AH, Houterman S, Tan ME, Soliman Hamad MA. Mid-Term Haemodynamic and Clinical Results after Aortic Valve Replacement Using the Freedom Solo Stentless Bioprosthesis versus the Carpentier Edwards Perimount Stented Bioprosthesis. Eur J Cardiothorac Surg. 2016;49(4):1174-80. doi: 10.1093/ejcts/ezv255.

31. Gersak B, Fischlein T, Folliguet TA, Meuris B, Teoh KH, Moten SC, et al. Sutureless, Rapid Deployment Valves and Stented Bioprosthesis in Aortic Valve Replacement: Recommendations of an International Expert Consensus Panel. Eur J Cardiothorac Surg. 2016;49(3):709-18. doi: 10.1093/ejcts/ezv369.

32. Pibarot P, Weissman NJ, Stewart WJ, Hahn RT, Lindman BR, McAndrew T, et al. Incidence and Sequelae of Prosthesis-Patient Mismatch in Transcatheter versus Surgical Valve Replacement in High-Risk Patients with Severe Aortic Stenosis: A PARTNER Trial Cohort--A Analysis. J Am Coll Cardiol. 2014;64(13):1323-34. doi: 10.1016/j.jacc.2014.06.1195.

33. Panoulas VF, Chandrasekhar J, Busi G, Ruparelia N, Zhang Z, Mehilli J, et al. Prevalence, Predictors, and Outcomes of Patient Prosthesis Mismatch in Women Undergoing TAVI for Severe Aortic Stenosis: Insights from the WIN-TAVI Registry. Catheter Cardiovasc Interv. 2021;97(3):516-526. doi: 10.1002/ccd.29227.

34. Sato K, Seo Y, Ishizu T, Nakajima H, Takeuchi M, Izumo M, et al. Reliability of Aortic Stenosis Severity Classified by 3-Dimensional Echocardiography in the Prediction of Cardiovascular Events. Am J Cardiol. 2016;118(3):410-7. doi: 10.1016/j.amjcard.2016.05.016.

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(4):1131-41. doi: 10.1016/s0735-1097(00)00859-7.

36. Sohn SH, Jang MJ, Hwang HY, Kim KH. Rapid Deployment or Sutureless versus Conventional Bioprosthetic Aortic Valve Replacement: A Meta-Analysis. J Thorac Cardiovasc Surg. 2018;155(6):2402-2412.e5. doi: 10.1016/j.jtcvs.2018.01.084.

37. Berretta P, Andreas M, Carrel TP, Solinas M, Teoh K, Fischlein T, et al. Minimally Invasive Aortic Valve Replacement with Sutureless and Rapid Deployment Valves: A Report from an International Registry (Sutureless and Rapid Deployment International Registry)†. Eur J Cardiothorac Surg. 2019;56(4):793-9. doi: 10.1093/ejcts/ezz055.

38. Vlastra W, Chandrasekhar J, Vendrik J, Gutierrez-Ibanes E, Tchétché D, Brito FS Jr, et al. Transfemoral TAVR in Nonagenarians: From the CENTER Collaboration. JACC Cardiovasc Interv. 2019;12(10):911-20. doi: 10.1016/j.jcin.2019.02.031.

39. Tribouilloy C, Bohbot Y, Rusinaru D, Belkhir K, Diouf M, Altes A, et al. Excess Mortality and Undertreatment of Women with Severe Aortic Stenosis. J Am Heart Assoc. 2021;10(1):e018816. doi: 10.1161/JAHA.120.018816.

40. Vlastra W, Chandrasekhar J, García Del Blanco B, Tchétché D, Brito FS Jr, et al. Sex Differences in Transfemoral Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2019;74(22):2758-67. doi: 10.1016/j.jacc.2019.09.015.

41. O'Connor SA, Morice MC, Gilard M, Leon MB, Webb JG, Dvir D, et al. Revisiting Sex Equality with Transcatheter Aortic Valve Replacement Outcomes: A Collaborative, Patient-Level Meta-Analysis of 11,310 Patients. J Am Coll Cardiol. 2015;66(3):221-8. doi: 10.1016/j.jacc.2015.05.024.

42. Siontis GC, Praz F, Pilgrim T, Mavridis D, Verma S, Salanti G, et al. Transcatheter Aortic Valve Implantation vs. Surgical Aortic Valve Replacement for Treatment of Severe Aortic Stenosis: A Meta-Analysis of Randomized Trials. Eur Heart J. 2016;37(47):3503-12. doi: 10.1093/eurheartj/ehw225.

43. Saad M, Nairooz R, Pothineni NVK, Almomani A, Kovelamudi S, Sardar P, et al. Long-Term Outcomes with Transcatheter Aortic Valve Replacement in Women Compared with Men: Evidence From a Meta-Analysis. JACC Cardiovasc Interv. 2018;11(1):24-35. doi: 10.1016/j.jcin.2017.08.015.

44. Pighi M, Ribichini F. Self-Expandable Transcatheter Heart Valves in Small Annuli: Does One Valve Fit All? JACC Cardiovasc Interv. 2020;13(2):207-9. doi: 10.1016/j.jcin.2019.09.035.

45. Herrmann HC, Abdel-Wahab M, Attizzani GF, Batchelor W, Bleiziffer S, Verdoliva S, et al. Rationale and Design of the SMall Annuli Randomized To Evolut or SAPIEN Trial (SMART Trial). Am Heart J. 2022;243:92-102. doi: 10.1016/j.ahj.2021.09.011.

46. Valvo R, Costa G, Barbanti M. How to Avoid Coronary Occlusion During TAVR Valve-in-Valve Procedures. Front Cardiovasc Med. 2019;6:168. doi: 10.3389/fcvm.2019.00168.

47. Kim WK, Möllmann H, Liebetrau C, Renker M, Rolf A, Simon P, et al. The ACURATE Neo Transcatheter Heart Valve: A Comprehensive Analysis of Predictors of Procedural Outcome. JACC Cardiovasc Interv. 2018;11(17):1721-9. doi: 10.1016/j.jcin.2018.04.039.

48. Chandrasekhar J, Dangas G, Yu J, Vemulapalli S, Suchindran S, Vora AN, et al. Sex-Based Differences in Outcomes with Transcatheter Aortic Valve Therapy: TVT Registry From 2011 to 2014. J Am Coll Cardiol. 2016;68(25):2733-44. doi: 10.1016/j.jacc.2016.10.041.

49. Carroll JD, Mack MJ, Vemulapalli S, Herrmann HC, Gleason TG, Hanzel G, et al. STS-ACC TVT Registry of Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2020;76(21):2492-516. doi: 10.1016/j.jacc.2020.09.595.

50. Stangl V, Baldenhofer G, Laule M, Baumann G, Stangl K. Influence of Sex on Outcome Following Transcatheter Aortic Valve Implantation (TAVI): Systematic Review and Meta-Analysis. J Interv Cardiol. 2014;27(6):531-9. doi: 10.1111/joic.12150.

51. Ribeiro HB, Webb JG, Makkar RR, Cohen MG, Kapadia SR, Kodali S, et al. Predictive Factors, Management, and Clinical Outcomes of Coronary Obstruction Following Transcatheter Aortic Valve Implantation: Insights from a Large Multicenter Registry. J Am Coll Cardiol. 2013;62(17):1552-62. doi: 10.1016/j.jacc.2013.07.040.

52. Barbanti M, Yang TH, Rodès Cabau J, Tamburino C, Wood DA, Jilaihawi H, et al. Anatomical and Procedural Features Associated with Aortic Root Rupture During Balloon-Expandable Transcatheter Aortic Valve Replacement. Circulation. 2013;128(3):244-53. doi: 10.1161/CIRCULATIONAHA.113.002947.

53. Bilkhu R, Jahangiri M, Otto CM. Patient-Prosthesis Mismatch Following Aortic Valve Replacement. Heart. 2019;105(Suppl 2):s28-s33. doi: 10.1136/heartjnl-2018-313515.

54. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease. Eur Heart J. 2017;38(36):2739-91. doi: 10.1093/eurheartj/ehx391.

55. Mahmoud AN, Gad MM, Elgendy IY, Mahmoud AA, Taha Y, Elgendy AY, et al. Systematic Review and Meta-Analysis of Valve-In-Valve Transcatheter Aortic Valve Replacement in Patients with Failed Bioprosthetic Aortic Valves. EuroIntervention. 2020;16(7):539-48. doi: 10.4244/EIJ-D-19-00928.

56. Bleiziffer S, Simonato M, Webb JG, Rodés-Cabau J, Pibarot P, Kornowski R, et al. Long-term Outcomes After Transcatheter Aortic Valve Implantation in Failed Bioprosthetic Valves. Eur Heart J. 2020;41(29):2731-42. doi: 10.1093/eurheartj/ehaa544.

57. Ternacle J, Guimaraes L, Vincent F, Côté N, Côté M, Lachance D, et al. Reclassification of Prosthesis-Patient Mismatch after Transcatheter Aortic Valve Replacement Using Predicted vs. Measured Indexed Effective Orifice Area. Eur Heart J Cardiovasc Imaging. 2021;22(1):11-20. doi: 10.1093/ehjci/jeaa235.

58. Landes U, Sathananthan J, Witberg G, De Backer O, Sondergaard L, Abdel-Wahab M, et al. Transcatheter Replacement of Transcatheter versus Surgically Implanted Aortic Valve Bioprostheses. J Am Coll Cardiol. 2021;77(1):1-14. doi: 10.1016/j.jacc.2020.10.053.

59. Allen KB, Chhatriwalla AK, Saxon JT, Cohen DJ, Nguyen TC, Webb J, et al. Bioprosthetic valve Fracture: Technical Insights from a Multicenter Study. J Thorac Cardiovasc Surg. 2019;158(5):1317-1328.e1. doi: 10.1016/j.jtcvs.2019.01.073.

60. Khan JM, Babaliaros VC, Greenbaum AB, Spies C, Daniels D, Depta JP, et al. Preventing Coronary Obstruction During Transcatheter Aortic Valve Replacement: Results From the Multicenter International BASILICA Registry. JACC Cardiovasc Interv. 2021;14(9):941-8. doi: 10.1016/j.jcin.2021.02.035.