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Review Article

Understanding Aortic Stenosis and Transcatheter Aortic Valve Replacement in Women

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ABSTRACT

The impact of sex on the baseline characteristics, morphology, and clinical presentation of degenerative aortic stenosis (AS) is well-documented but remains poorly understood. Unlike valve surgery, for which patients have been predominantly male, percutaneous treatment of AS has shown balanced representation of both sexes, with women demonstrating greater benefit from transfemoral aortic valve replacement compared to surgical treatment. This review explores sex-specific differences in the epidemiology, pathophysiology, diagnostic challenges, treatment approaches, and clinical outcomes of degenerative AS. Furthermore, it addresses technical, sex-specific considerations in transfemoral aortic valve replacement, including preprocedural screening, device selection, implantation strategy, and postprocedural management.

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ABBREVIATIONS

AS, aortic stenosis; AV, aortic valve; BEV, balloon-expandable valve; CAD, coronary artery disease; DOAC, direct oral anticoagulant; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; OAC, oral anticoagulation; RCTs, randomized controlled trials; SAVR, surgical aortic valve replacement; TAVR, transfemoral aortic valve replacement; THV, transcatheter heart valve.

Introduction

Sex-related differences in degenerative aortic stenosis (AS), the most prevalent valvular heart disease worldwide, are widely acknowledged.[1] Female patients are well represented in the transcatheter treatment of severe AS, as demonstrated by both national registries and landmark trials.[2] Indeed, research suggests that women may derive greater benefit than men with transfemoral aortic valve replacement (TAVR) compared to surgical treatment.[2] This review explores the influence and impact of female sex on the diagnosis and management of severe AS, incorporating the latest findings on its epidemiology, pathophysiology, clinical presentation, and treatment.[2,3] Moreover, it offers a comprehensive perspective on sex-specific technical aspects of TAVR and their potential impact on outcomes.

Understanding of Nonrheumatic Calcific Aortic Valve Disease in Women

Sex Differences in Epidemiology and Pathophysiological Features

Sex-dependent variation in epidemiological and pathophysiological features of AS, although extensively described, is still a subject of wide discussion[1] (Figure 1).

Historically, male sex has been suggested as a risk factor for calcific aortic valve (AV) disease,[4] with early echo studies suggesting a higher prevalence of AS in men, also potentially due to the 3 to 4 times higher prevalence of bicuspid disease.[5,6] However, more recent studies suggest an equal sex distribution or even a higher proportion of women affected by AS, especially in aging populations.[7–12] Indeed, due to the difference in life expectancy between the 2 sexes, with greater longevity for women, women are overrepresented among the oldest.

The pathophysiological mechanisms driving the development and progression of AS also appear to differ between men and women. The fundamental pathology involves an inflammatory process that culminates in calcification. Several studies have demonstrated a lower degree of calcification in women as compared to men with a similar hemodynamic severity of AS.[13–15] Yet women tend to have a more diffuse pattern of fibrosis.[16] The specific pathophysiological mechanisms are still not clearly understood but have been hypothesized to be driven by intrinsic differences in various inflammatory and growth factor-related pathways.[17,18] On a molecular level, there is a greater inflammatory response to interferon-α activity and lipopolysaccharides in men compared with women. It is theorized that a female-specific kinase protects interstitial cells from mineralization in women, hence the lower rate of calcification.[17] Interestingly, 183 gene differences have been identified to impact the aging processes on a cellular level in men and women, such as proliferation, apoptosis, ossification, and angiogenesis.[19] Indeed, for the same disease severity, women have a lower degree of AV calcification than men, even after indexing to body surface area or aortic annular area.[13,15,20,21] Furthermore, after adjustment for age, body mass index, AV calcification density, and aortic annulus diameter, women appear to have a significantly greater degree of fibrosis compared to men.[13]

Differences in the patterns of the left ventricular (LV) response to AS have also been a subject of recent debate.[22–32] Given the association that has been established between LV hypertrophy (concentric hypertrophy and increased LV wall thickness) and worse outcomes in AS,[33–35] identifying a potential relationship with sex has been an important goal. Many early echocardiographic studies investigating the LV geometric phenotype in AS suggested a higher prevalence of concentric hypertrophy in women and a more eccentric, dilated ventricular response in men.[22–26] However, this has been contested by more recent studies, especially those utilizing cardiac magnetic resonance, which have shown either no significant differences in remodeling patterns[27] or even a higher prevalence of concentric phenotypes in men, with a higher LV remodeling index (LV mass index/LV end diastolic volume).[16,28–32] Beyond differences in the prevalence of geometric phenotypes, evidence suggests that concentric hypertrophy exerts a sex-specific impact on clinical outcomes. In particular, this remodeling pattern appears to be more strongly linked to adverse outcomes—and especially to increased mortality—in women compared to men.[34] This may reflect the more pronounced maladaptive response to pressure overload in females,

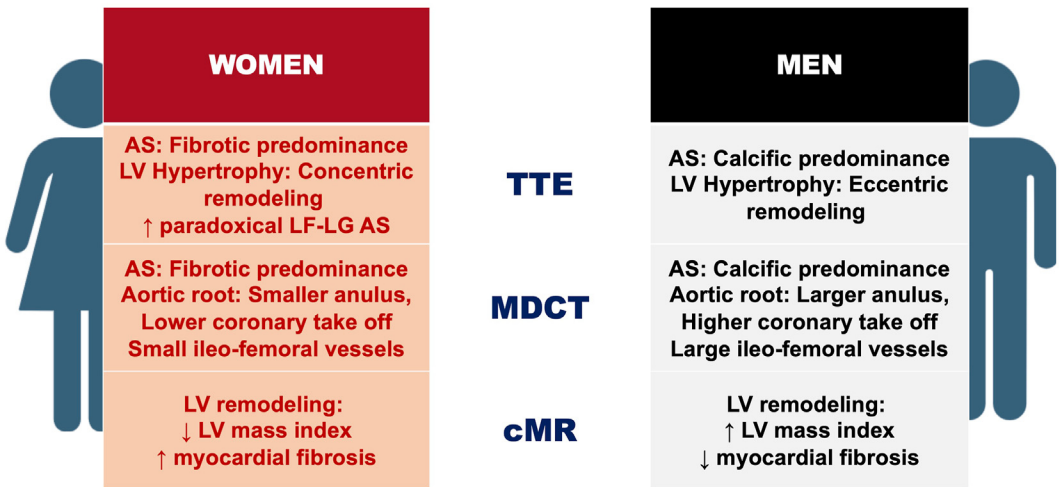

Figure 1. Illustrative representation of different aortic valve phenotypes in men and women according to diagnostic modalities.
Abbreviations: AS, aortic stenosis; cMR, cardiac magnetic resonance; LF-LG AS, low-flow low-gradient aortic stenosis; LV, left ventricle; MDCT, multidetector computed tomography; TTE, transthoracic echocardiography.

characterized by a more important reduction in LV cavity size, a decrease in LV compliance and impairment of LV filling and pump function, and a higher susceptibility to heart failure with preserved LV ejection fraction (LVEF).

Indeed, other structural differences of the LV have also been observed to extend to differences in flow status. Women have been found to more commonly have a preserved LVEF in combination with a low stroke volume index and a lower mean pressure gradient.[26] This correlates to the finding of paradoxical low-flow low-gradient AS, which has been found to be more common in women.[9,36] This phenotype has been repeatedly associated with worse outcomes, an association that also appears to be stronger in women, particularly after aortic valve replacement (AVR).[37,38] These associations, however, have also not gone without challenge, as other studies have found that women more commonly presented with the less severe normal-flow low-gradient variant.[39]

Sex Differences in Baselines, Clinical Presentation, and Diagnostic Assessment

At presentation (Figure 2), women tend to be older, have a lower body mass index, have a higher frailty index, and suffer more frequently from chronic kidney disease, hypertension, and anemia.[15,40–42] The occurrence of concurrent mitral and tricuspid valve disease is also higher in women, whereas women with AS have a lower incidence of concomitant coronary artery disease (CAD) than men. In addition, women usually have a more advanced New York Heart Association class and a shorter exercise capacity. Moreover, symptoms such as shortness of breath and reduced activity are frequently overlooked by both patients and bystanders, as they are often misattributed to normal aging, resulting in delayed diagnosis and referral for treatment. The overall Society of Thoracic Surgeons score is generally higher. Although women have a higher LVEF, they have a lower stroke volume index, and therefore, paradoxical low-flow low-gradient AS is more common in women, which is not only difficult to diagnose but also has a worse prognosis and higher periprocedural mortality.[43] In terms of disease progression, women with mild to moderate AS have a slower progression of AS and lower referral for aortic valve replacement (AVR); however, no sex-based difference in mortality has been reported.[44,45] Prolonged pressure overload due to AS leads to upstream myocardial damage, which negatively impacts prognosis. A staging classification has recently been introduced to semi-quantitatively assess the extent of extra-aortic valve cardiac damage and has proven useful for stratifying long-term survival after AVR, regardless of sex. However, a favorable association between female sex and long-term survival was observed only in the early stages of damage (stages 0, 1, or 2), but not in advanced stages (stages 3 or 4).[46]

Despite known differences in the morphology of the AV, sex-specific diagnostic cutoffs are still lacking, especially in important echocardiographic measures of AS severity and in cardiac flow state evaluation.[47,48] Although the current European Society of Cardiology guidelines recognize sex-specific cutoffs for diagnosing severe AS through calcification measurements on cardiac computed tomography, no such differentiated cutoffs exist in important echocardiographic measures such as peak velocity, valve area, and mean pressure gradient.[49] Moreover, women usually have smaller annuli and aortic roots. This is especially important given the known impact of the smaller AVs observed in women on the diagnostic accuracy of measurements such as AV area and left ventricular outflow tract (LVOT) diameter.[42,50] As previously elucidated, another important difference to capture is the LV remodeling and myocardial fibrosis pattern, which is usually more concentric and restrictive in women.[16,51,52] Therefore, the LV is less likely to dilate in women.[10] A Simvastatin and Ezetimibe in Aortic Stenosis substudy revealed smaller volumes and dimensions, higher filling pressures, and more advanced diastolic dysfunction in women.[53] This was further confirmed by cardiac magnetic resonance imaging, noting that women had a higher LVEF compared with men (61% in women and 55% in men).[11] Although women have a smaller LV mass index compared with men, their extracellular volume fraction is larger. Furthermore, late gadolinium enhancement often detects irreversible focal fibrosis at an earlier stage in women.[11,15]

Understanding of Transcatheter Aortic Valve Replacement in Women

Surgical vs. Transcatheter Approach in Female Patients

Female patients underwent surgical intervention at a significantly older age (75 vs. 71 years), and the procedure was more frequently declined in this group due to advanced age, patient refusal, or symptom relief following conservative treatment.[54] It has been shown that women are diagnosed at a more advanced state of the disease, displaying a higher symptomatic burden and a higher rate of heart failure, which might be due to a lack of awareness of patients as well as physicians.[42,55,56] Even after diagnosis, women face longer workup and procedural waiting times, resulting in higher 30-day mortality and heart failure

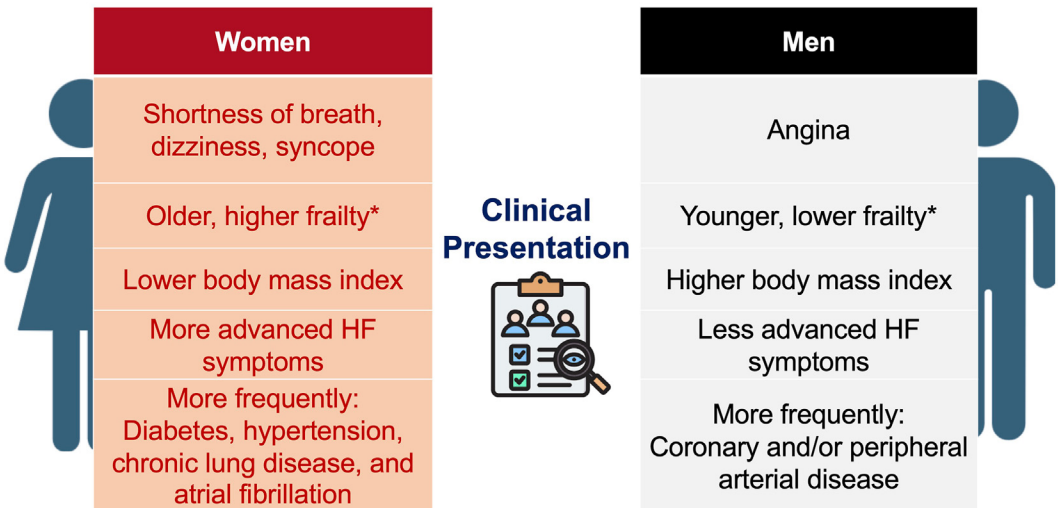

Figure 2. Illustrative representation of different clinical presentation of significant aortic stenosis in men and women. *Frailty in Older Adults Undergoing Aortic Valve Replacement Index.
Abbreviation: HF, heart failure.

hospitalization than men.[57] A recent analysis confirmed that female patients across Europe were less likely than males to receive surgical or interventional treatment. Interestingly, however, women were significantly more likely to undergo TAVR.[58] In this context, the role of heart failure medications (i.e., sodium-glucose cotransporter 2 inhibitors) in slowing disease progression or aiding postprocedural management remains to be fully established.[59]

Evidence about sex-related differences in outcomes after different AV stenosis treatments can be derived from subanalyses of large trials comparing surgical aortic valve replacement (SAVR) vs. TAVR. In particular, the subanalysis of the Placement of Aortic Transcatheter Valves (PARTNER) I trial evaluated sex-specific differences in outcomes after TAVR with balloon-expandable valve (BEV) vs. SAVR in high-risk female patients with severe symptomatic AS. Three hundred female patients (43% of the whole study population) were included in the analysis, with a follow-up of 2 years. Compared to men, women presented higher risk scores but lower comorbidity rates for CAD, peripheral artery disease, diabetes, and renal impairment at baseline. According to these significant differences in important comorbid conditions, outcomes showed a lower procedural mortality rate in women after transfemoral TAVR when compared to SAVR, and the result was consistent up to 6 months and 2 years of follow-up. Nevertheless, women reported a higher periprocedural stroke rate after percutaneous treatment than surgery.[60] In a post hoc analysis of the randomized Surgical or Transcatheter Aortic Valve Replacement in Intermediate Risk Patients (SURTAVI) trial, comparing outcomes after TAVR or SAVR in 1660 women and men at intermediate risk, women underwent less frequent concomitant coronary revascularization, and the functional status improvement after valve intervention in women appeared to be greater after TAVR than SAVR.[61] A recent comparison between 514 women and 441 men undergoing percutaneous or surgical treatment for AS showed no difference in mortality or major postoperative complication rates after both procedures between the female and male populations. Nevertheless, women were older and had higher EuroSCORE II.[62] In a meta-analysis of the sex-specific results of randomized controlled trials (RCTs) comparing TAVR with SAVR, women undergoing TAVR had a significantly lower mortality than SAVR recipients at 1 year and at 2 years, while no difference in mortality between TAVR and SAVR was observed in male patients. The difference in treatment effect was significant at both 1 year (p interaction = 0.02) and 2 years (p interaction = 0.04).[63]

Recently, the VIVA trial reported no evidence of superiority of contemporary TAVR vs. SAVR in clinical outcomes and valve hemodynamic results up to 2 years of follow-up in patients with severe AS and small aortic annuli (women in the majority).[64] The RHEIA Trial (Randomized researcH in womEn all comers wIth Aortic stenosis) is the first investigator-initiated, multicenter, international randomized trial directly comparing TAVR with BEV and SAVR outcomes in a population of solely women with symptomatic AS.[65] Exclusion criteria included bicuspid AV, noncalcified AV, complex CAD, and other anatomical features increasing the risk of complications with TAVR or surgery. A total of 440 patients were randomized to TAVR with the SAPIEN 3 or SAPIEN 3 Ultra device or SAVR with any commercially available surgical valve at 48 sites across 12 countries. The primary endpoint was a composite of all-cause mortality, stroke, and rehospitalization for valve- or procedure-related symptoms or worsening heart failure within 1 year of randomization and occurred in 8.9% and 15.6% of TAVR and SAVR patients, respectively (hazard ratio: 0.55, 95% CI: 0.34-0.88, $p = 0.03$), proving the superiority of TAVR over SAVR. It was mainly driven by a lower rate of valve-related or procedure-related or worsening congestive heart failure rehospitalizations. Among secondary outcomes, women receiving TAVR had a lower incidence of new-onset atrial fibrillation at 30 days and a shorter length of hospital stay but higher rates of mild paravalvular aortic regurgitation (AR) and new permanent pacemaker implantation. Looking at echocardiographic assessment, the occurrence of 30-day patient-prosthesis mismatch and 1-year paravalvular AR were similar, but the mean gradient was significantly lower with larger effective orifice area after SAVR.

TAVR Outcomes in Female Patients vs. Male Patients

The safety and efficacy of TAVR in female patients can be assessed through subgroup analyses of RCTs and observational studies (Figure 3, Table 1). Women represented approximately 50% of the patients at increased surgical risk included in the pivotal TAVR studies.[75] However, they are underrepresented in low-risk studies, accounting for only about 33%.[76,77]

In the secondary analysis of historical RCTs, women experienced higher 30-day rates of bleeding and vascular complications after TAVR, showing comparable or lower early and 1-year survival and stroke incidence compared to men.[66–68]

The Women's International Transcatheter Aortic Valve Implantation registry, the first global, multicenter, prospective study involving 1019 women who underwent TAVR between 2013 and 2015, reported an average age of 82.5 ± 6.3 years and a mean LVEF of 55.7% ± 10.7%. Approximately 90% of the patients were deemed high-risk for surgery. Transfemoral TAVR was performed in 90.6% of cases, with 42.1% utilizing new-generation valves. At 30 days, the primary Valve Academic Research Consortium-2 early safety endpoint occurred in 14% of cases,

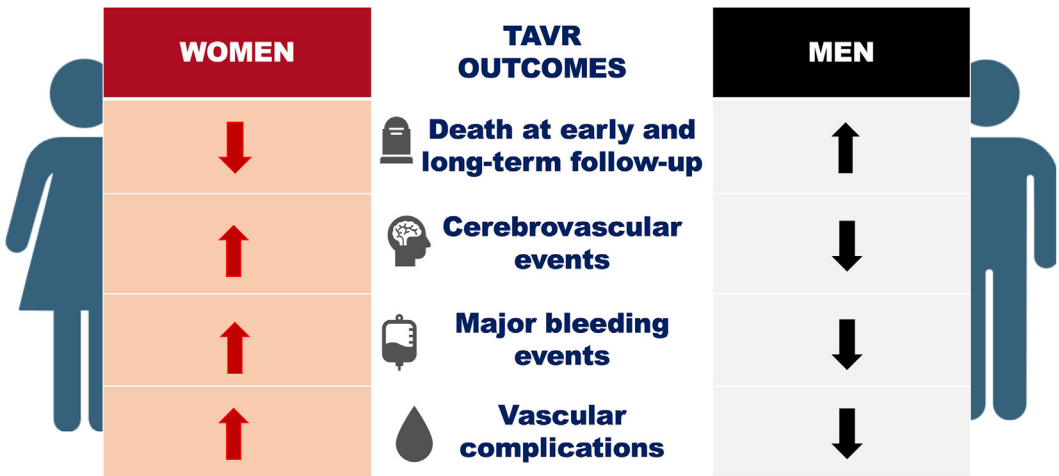

Figure 3. TAVR outcomes in women vs. men: summary of evidence.
Abbreviation: TAVR, transcatheter aortic valve replacement.

Table 1
Studies showing the main clinical outcomes after TAVR in women

Study/first author and design (ref)	Overall population (n)	% Women	Mean age		Operative risk (%)		Follow-up	Vascular complications (%)		Major bleeding (%)		All-cause mortality (%)		Stroke (%)	
			Women	Men	Women	Men		Women	Men	Women	Men	Women	Men	Women	Men
Kodali et al.[66] analysis of RCT	2559	47.6	84.9 ± 6.9	84.1 ± 7.3	11.9 ± 4.2	11.1 ± 4.0	30-d	17.3	5.1	10.5	7.7	6.5	5.9	3.8	3.0
							1-y	-	-	-	-	19.0	25.9	-	-
Forrest et al.[67] analysis of RCT	3687	46.3	84.0 ± 7.6	82.7 ± 7.9	20.7 ± 15.0*	23.4 ± 16.5*	30-d	9.7	4.9	29.7	21.7	5.9	5.8	5.7	4.0
							1-y	9.9	5.3	32.1	25.4	24.1	21.3	9.3	7.7
Szerlip et al.[68] analysis of RCT	1661	39.5	82.5 ± 7.2	82.0 ± 7.1	6.8 ± 3.0	6.3 ± 2.8	1-y	7.2	4.2	16.7	14.6	9.4	10.4	2.4	2.3
WIN-TAVI Registry[69,70]	1019	100	82.5 ± 6.3	-	8.3 ± 7.4	-	30-d	7.7	-	12	-	3.4	-	1.3	-
							1-y	8.2	-	12.9	-	12.5	-	2.2	-
TVT Registry[71]	23,652	49.9	82.3 ± 8.5	81.7 ± 8.6	9 ± 6	8 ± 6	1-y	8.3	4.4	8.0	5.9	21.3	24.5	4.6	3.4
Buchanan et al.[72] Registry	305	47.9	80.1 ± 6.8	78.8 ± 7.8	9.1 ± 7.9	8.2 ± 7.8	30-d	19.9	11.9	35.8	30.1	5.6	3.8	0.7	1.3
Saad et al.[73] Meta-Analysis	47,188	49.4	82.7 ± 1.2	81.8 ± 1.4	20.3 ± 5.3*	22.2 ± 5.7*	30-d	RR 1.37; 95% CI (1.26-1.49)		RR 1.62; 95% CI (1.35-1.95)		6.5	6.2	RR 1.28; 95% CI (1.04-1.57)	
							1-y	-	-	-	-	16.0	19.4	-	-
Kumar et al.[74] PSM Registry	165,894	50.0	81.1 ± 11	80.0 ± 12	-	-	In-H	1.2	0.7	2.3	1.7	2.5	2.1	2.1	1.5

Abbreviations: In-H, in-hospital; PSM, propensity score match; RCT, randomized controlled trial; RR, risk ratio; TAVR, transcatheter aortic valve replacement; TVT, Transcatheter Valve Therapy; WIN-TAVI, Women's International Transcatheter Aortic Valve Implantation.

* Logistic EuroScore; all the other risk scores are reported as Society of Thoracic Surgeons scores.

mainly driven by vascular complications (7.7%) and bleeding (4.4%). Key predictors of this primary endpoint included advanced age, prior stroke, LVEF <30%, use of new-generation devices, and a history of pregnancy.[69] After 1 year, the primary efficacy endpoint was observed in 16.5% of patients, with mortality and stroke rates of 12.5% and 2.2%, respectively.[70]

In the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry, compared with male patients, female patients were older, with a lower prevalence of CAD, atrial fibrillation, and diabetes but a higher rate of porcelain aorta, lower glomerular filtration rate, and higher mean Society of Thoracic Surgeons score. In-hospital vascular complications were more frequent in women, and a trend toward higher bleeding was observed; however, 1-year mortality was lower in women than in men.[71] Similarly, data from the Milan Registry showed that female sex was a predictor of major vascular complications; however, no differences were noted among patients undergoing TAVR in composite safety and efficacy endpoints according to sex.[72]

In a meta-analysis of 17 observational studies (n = 47,188 patients, 49.4% women), women were older and had more bleeding, vascular complications, and stroke/transient ischemic attack at 30 days without difference in all-cause or cardiovascular mortality compared with men; notwithstanding, female sex was linked to better survival at 1 year and longest available follow-up (mean 3.28 ± 1.04 years), and this advantage remained consistent across multiple secondary analyses.[73]

In a propensity-matched analysis from the Nationwide Readmissions Database (2016-2020) stratified by sex, women had higher in-hospital mortality, stroke, postprocedural bleeding, vascular complications, pericardial complications, acute respiratory failure, need for transfusion, need for vasopressors, and major adverse cardiac and cerebrovascular events but a lower incidence of acute kidney injury, sudden cardiac arrest, cardiogenic shock, and mechanical circulatory support requirement. Men had higher readmission rates at 30 and 90 days. No significant difference was observed in 180-day readmission rates between men and women after TAVR.[74]

The interaction between specific TAVR devices and specific anatomic features of female patients has been explored in the Self-Expanding or Balloon-Expandable TAVR in Patients with a Small Aortic Annulus (SMART) Trial, in which 716 patients with small aortic annulus (defined as an AV annulus area of 430 mm^2 or less) were randomly assigned to undergo TAVR with either a self-expanding supra-annular valve or a BEV; women account for 87% of total participants. The Kaplan-Meier estimate of the first co-primary endpoint including death, disabling stroke, or rehospitalization for heart failure through 12 months, was 9.4% with the self-expanding valve and 10.6% with the BEV (difference: −1.2% points; 90% CI: −4.9 to 2.5; $p < 0.001$ for noninferiority). The Kaplan-Meier estimate of the secondary co-primary endpoint of bioprosthetic-valve dysfunction (bioprosthetic valve dysfunction, defined as mean gradient ≥20 mm Hg, severe prosthesis-patient mismatch, or ≥ moderate AR, thrombosis, endocarditis, or reintervention) through 12 months was 9.4% with the self-expanding valve and 41.6% with the BEV (difference: −32.2% points; 95% CI: −38.7 to −25.6; $p < 0.001$ for superiority).[78] Additional evidence indicated that among patients with a similarly sized aortic annulus, self-expanding valves show lower Doppler-derived AV gradients compared to BEVs. However, this difference disappears when invasive-derived AV gradients are compared between self-expanding and BEVs. Consequently, it remains uncertain whether the second co-primary outcome in this trial would have differed if invasive gradients, rather than Doppler gradients, were assessed. Moreover, the relatively short follow-up period might not have been sufficient to identify differences in clinical outcomes between the 2 valve types.

The recent emergence of female sex-specific clinical trials reflects a growing recognition of sex-related differences in cardiovascular disease and marks a pivotal shift toward more tailored and inclusive research in AS.[64,65,78]

Anatomical Considerations for TAVR Procedure in Female Patients: An Integrative Approach

The contemporary TAVR planning and lean procedure follows established standards of effectiveness for both sexes.[79] However, considering the distinctive anatomical characteristics and pathophysiological features of AS in females and their longer life expectancy, it is particularly advisable to tailor transcatheter heart valve (THV) choice and implantation strategy in order to minimize adverse events, optimize valve performance, and foster future valve reintervention in a sex-oriented approach[2] (Figure 4).

As previously highlighted, females present more often with a small anatomic root (including small annulus, sinus of Valsalva, and sinotubular junction), low coronary ostia, small and hypercontractile LV cavity, and small ileo-femoral vessels resulting in an unfavorable "sheath-to-femoral artery ratio," together with a small body surface area. Moreover, accumulating evidence suggests, in comparison to men, a higher prevalence of AV fibrosis than calcification and more frequent paradoxical low-flow low-gradient AS phenotypes in female patients. These characteristics correlate with peculiar risk, including a higher incidence of bleeding and vascular complications, an increased likelihood of acute coronary occlusion (due to the displacement of the calcified leaflet over the coronary ostia or the sinus of Valsalva sequestration at the sinotubular junction), greater residual postprocedural gradients and patient-prosthesis mismatch, a higher rate of LV perforation, and a more severe impact of residual paravalvular leak and conduction disorders.[2]

First and foremost, a careful assessment of all the above-mentioned parameters should be performed with a multimodality imaging evaluation and, in particular, by means of a multi-slice computed tomography.[80] Moreover, recent advances in computational modeling and computer simulation technologies have been introduced to optimize THV selection and procedural planning, offering a patient-specific approach.[81]

The currently available THVs are designed to cover specific annulus size ranges; however, based on manufacturer recommendations and sizing charts, not all devices accommodate the smallest annular dimensions (<21 mm). When selecting a device type, current evidence on TAVR in small annuli suggests that THVs with supra-annular leaflet attachment may be advantageous in such anatomies, as they can help achieve a larger effective orifice area and a lower transvalvular gradient.[68] However, clinical data on the long-term impact of suboptimal hemodynamic performance after TAVR are still lacking.[82,83] On the other hand, the high sealing skirts of supra-annular devices can pose challenges in selectively cannulating the coronary arteries, particularly in patients with a small sinotubular junction, which underscores the importance of achieving precise commissural alignment. For patients at increased risk of needing subsequent TAVR-in-TAVR procedures or percutaneous coronary intervention, a balloon-expandable, intra-annular short-frame device may be preferable. Lastly, the delivery sheath profile must also be considered, and in cases of suboptimal vascular access, a THV with a low-profile delivery system should be selected.

Regarding procedural steps, special attention must be paid to the combined ultrasound- and fluoroscopy-guided puncture and adequate use of vascular closure device for percutaneous closure of the primary access, along with a minimalistic approach with a diagnostic radial access with possible crossover technique for controlled angiography and balloon inflation of the therapeutic access.[2] To enable secure and stable positioning, operators who are accustomed to shaping the tip of their wire should apply a smaller loop at the distal end or, otherwise, choose a dedicated preshaped rigid guide wire with a small curve.[84] Accurate procedural planning requires the recognition of anatomical predictors of high coronary obstruction risk, especially in female patients who tend to have smaller aortic anatomy and lower coronary ostia: native or bioprosthetic aortic leaflet length that extends above the coronary ostia or above the sinotubular junction; a coronary artery height ≤10 mm; a virtual valve to coronary artery/to sinotubular junction distance of ≤4 mm and ≤2 mm, respectively; and degenerative stentless bioprosthetic valve or with externally mounted leaflets. Accordingly, operators should consider simultaneous angiography if pre-TAVR balloon

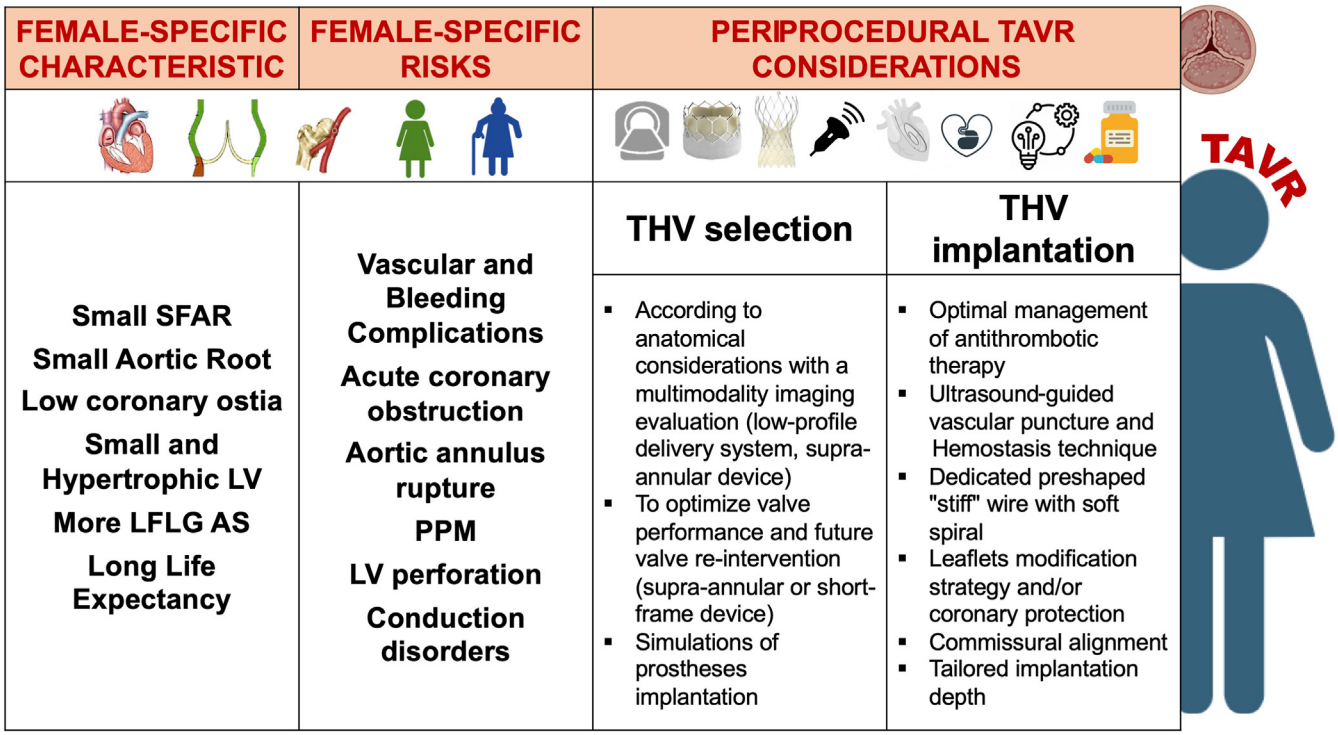

Figure 4. Periprocedural considerations for TAVR procedure in female patients: an integrative approach.
Abbreviations: LFLG AS, low-flow low-gradient aortic stenosis; LV, left ventricle; PPM, patient-prosthesis mismatch; SFAR, sheath-to-femoral artery ratio; TAVR, transcatheter aortic valve replacement; THV, transcatheter heart valve.

valvuloplasty is required, use of a repositionable/retrievable self-expandable THVs with a concave-shaped nitinol frame at the level of coronary arteries, aortic leaflet modification strategies such as the Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery Obstruction (BASILICA), and/or technical strategies for coronary patency protection (i.e., guiding catheter placement, guidewire placement, prepositioned stent ready to be deployed after TAVR in a chimney or snorkel fashion, or orthotopic stent strategy).[85,86]

Irrespective of the risk of coronary obstruction, it is particularly advisable to customize the implantation strategy of self-expandable supra-annular device (when selected) in order to foresee coronary recannulation and future valve reintervention.[87–89] Accordingly, strategies for commissural alignment must be implemented. Moreover, this prosthesis implantation depth should be tailored in order to minimize the risk of pacemaker implantation after the index procedure and prevent sinus sequestration in future TAVR-in-TAVR interventions. On the other hand, in the case of short-frame THV device selection, a slightly deeper implantation into the LVOT can be attempted to keep the neo-commissural plane below the coronary ostia plane. Although women are less likely than men to require permanent pacemaker implantation following TAVR—despite the underlying mechanisms being not fully understood—it is well established that left bundle branch block and pacing-induced dyssynchrony are poorly tolerated in the setting of a small, hypertrophic LV.[90] When pacing is required, the most physiological modality should be prioritized, with preservation of atrial contribution whenever possible. In this regard, multi-slice computed tomography-based measurement of membranous length enables a patient-specific approach to implantation depth, as placing the device at a depth shorter than the membranous septum length has been associated with a significantly lower risk of permanent pacemaker implantation.[91] Women are more likely to present with a prominent septal bulge, which may be associated with dynamic LVOT obstruction, potentially leading to the so-called "suicide ventricle" following TAVR. In such anatomies, a careful assessment is needed to determine whether SAVR may offer a safer alternative or if TAVR remains the only feasible option. In patients with significant LVOT obstruction undergoing TAVR, preemptive alcohol septal ablation has been proposed as an effective strategy to reduce the risk of postprocedural hemodynamic collapse, although no data currently support the use of 1 valve type over another in this setting.[92] Finally, residual gradient and leak should be accurately detected by multimodality evaluation (including supra-aortic angiogram, intraprocedural echocardiogram evaluation, aortic and LV invasive pressure measurements, and AR index) to try to optimize the hemodynamic result by means of adjunctive maneuvers.[93]

Antithrombotic Management After TAVR

The pharmacological management of antithrombotic therapy before and after TAVR is crucial due to the high risk of thromboembolic and bleeding complications.[76,94] Recent trials have provided significant insights into optimal strategies, showing that in patients without an indication for oral anticoagulation (OAC), single antiplatelet therapy with aspirin alone is preferable over dual antiplatelet therapy and over aspirin plus direct oral anticoagulants (DOACs), as it reduces bleeding risk without compromising efficacy in preventing cardiovascular events.[95–97] For patients with an OAC indication, the combination of OAC and antiplatelet therapy is linked to higher bleeding risks, and OAC alone is recommended.[98] While several RCTs have compared vitamin K antagonists and DOAC, none have conclusively established the superiority of DOACs in TAVR patients.[99,100] European guidelines currently recommend after TAVR life-long single antiplatelet therapy (Ia) or OAC in the case of patients who have other indications for OAC (Ia); dual antiplatelet therapy should be administered only in case of recent percutaneous coronary intervention.[49] Sex differences play an important role in TAVR outcomes, though specific guidelines for women are lacking, particularly regarding antithrombotic therapy, and very few sex-specific subanalyses were reported from RCTs. Women, who represent roughly half of patients undergoing TAVR, generally experience different rates of adverse events compared to men, with higher postprocedural rates of bleeding, vascular complications, and stroke. However, despite these complications, women tend to have better long-term survival outcomes.[65,71,101] The difference in pharmacokinetic and pharmacodynamic responses to antithrombotic therapies between men and women has already been well documented, particularly the increased risk of bleeding in women, which should be considered when choosing the appropriate antithrombotic regimen.[102] Sex disparities in the prescription of antithrombotic therapies have also been observed. Women are more likely to receive clopidogrel and less likely to be prescribed warfarin in the presence of CAD and atrial fibrillation (AF), respectively, potentially reflecting their lower prevalence of AF.[102] These differences may impact clinical outcomes, particularly given that women are more likely to develop anemia, a condition that has been associated with worse long-term prognoses in elderly women undergoing TAVR.[103,104] In the case of OAC therapy, particular attention should be paid to hemoglobin values, and an accurate re-evaluation of the thrombotic and bleeding risks might be suggested during follow-up. Up to 40% of women undergoing TAVR have AF, which is linked to an increased risk of death and stroke within 1 year.[71,73,101] In the Edoxaban vs. Vitamin K Antagonist for Atrial Fibrillation after TAVR (ENVISAGE AF) Trial, where 1377 patients (47.8% women) were enrolled, the risks of ischemic events and major bleeding were found to be similar between men and women. When comparing edoxaban to vitamin K antagonist, the risk of net adverse clinical events was comparable for both sexes. While both sexes experienced an increased risk of major bleeding with edoxaban, this risk was less pronounced in women compared to men, possibly due to a higher likelihood of receiving an adjusted dose and lower overall adherence to therapy.[105] In the ATLANTIS study (Anti-Thrombotic Strategy to Lower All Cardiovascular and Neurologic Ischemic and Hemorrhagic Events after Trans-Aortic Valve Implantation for Aortic Stenosis), which included 1500 TAVR patients, over half of whom were women, no significant differences were found between apixaban and the standard of care in terms of ischemic or bleeding outcomes for patients with an indication for OAC.[99] The subanalysis of the POPular TAVI (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation) trial, which was a randomized clinical trial to test the hypothesis that monotherapy with aspirin or OAC after TAVR is safer than the addition of clopidogrel (including a total of 978 patients—47.6% were women), showed similar overall bleeding and comparable composite of myocardial infarction and stroke rates between sexes.[106,107] However, major or life-threatening bleeding occurred more often in women vs. men, most of which were access-site bleedings. The use of aspirin pre- and post-TAVR increased major or life-threatening bleeding in women but not in men.

Given that bleeding and vascular complications are critical concerns for women undergoing TAVR, it is essential that antithrombotic and anticoagulant therapy be tailored to individual patient characteristics, including existing comorbidities and the potential for polytherapy that may heighten bleeding and thrombosis risks. Overall, further evidence from large clinical trials exploring the safety and efficacy balance of various antithrombotic strategies based on sex is needed to enhance therapeutic decision-making in daily clinical practice.

Frailty and Undertreatment

Undertreatment of female patients with severe AS remains a major concern. It is linked to both delayed diagnosis and lack of treatment. Previous observational studies have shown that women tend to be diagnosed at later ages and to be more symptomatic than men at the time of diagnosis despite fewer comorbidities. After being diagnosed with severe AS, women tend to experience lower survival rates compared to the expected survival of their peers in the general population.[108] One of

the potential reasons for this delay is the underestimation of the disease and symptoms by female patients, leading to a delay in seeking medical advice.[109] Additional considerations should be given to the impact of social support on patient engagement, as reluctance to undergo diagnostic workup or intervention for AS may, in part, reflect limited social resources or support networks.[110] The advanced age at diagnosis has various implications on the decision to treat, mainly related to the risk of frailty and fear of advanced age, with fewer referrals to specialist care and diagnostic tests compared to male patients, according to data gathered from the United States administrative claim databases.[56] An analysis from the English Hospital Episode Statistics found that female sex as well as minority ethnicity and social deprivation were associated with reduced access to SAVR or TAVR.[111] Moreover, in the case of procedure, these groups showed a reduced rate of timely procedure.

Frailty affects up to 50% of patients with an indication for intervention and is a legitimate concern.[112,113] In patients undergoing TAVR, frailty has indeed been associated with worse early and late outcomes, being a predictor of mortality, disability, periprocedural bleeding, increased length of hospital stays, and readmissions.[114,115] A study demonstrated that prefrail elderly patients are the best candidates for TAVR/SAVR, while advanced frailty levels, comorbidity, disability, cognitive impairment, and malnutrition increase patients' vulnerability to poorer outcomes after cardiovascular procedures, making palliative care the most appropriate option.[116] Moreover, although numerous studies have reaffirmed the prognostic value of frailty in patients undergoing TAVR, further research is needed to explore its treatability (i.e., synergistic combination of exercise and protein-rich oral nutritional supplementation for improving physical and mental facets of frailty).[117] There are currently strong recommendations for objective frailty assessment during pre-TAVR evaluation; however, so far there is no standardized and objective approach to diagnose frailty as a clinical syndrome.[115,118] Commonly used markers of frailty currently include age-associated declines in lean body mass, strength, endurance, balance, walking performance, and low activity.[119] The Essential Frailty Toolset score is widely used for frailty assessment in patients undergoing AVR due to its simplicity, clinical applicability, and strong prognostic value for both short- and long-term outcomes.[120] Decisions on AS in elderly patients should consider biological age and a comprehensive geriatric assessment, rather than just chronological age, to determine the most suitable treatment approach—TAVR, SAVR, or conservative medical therapy.[49] Regardless of these considerations, the best approach to reverse undertreatment of female patients with severe AS seems to be an earlier diagnosis. Raising awareness regarding the risks and prevalence of AS is key. Several initiatives have been developed in this regard, one of the most widespread being the Valve for Life initiative initiated in 2015 and aiming to facilitate access to novel therapies such as THV interventions and reduce age and sex discrimination in access to care (Valve for Life Initiative—escardio.org). In parallel, ongoing clinical trials in patients with moderate AS may also help prevent undertreatment by evaluating the benefit of earlier therapeutic intervention in populations that have traditionally been overlooked.[121,122]

Conclusions and Future Perspectives

It is widely acknowledged that women with AS undergoing TAVR exhibit distinct pathophysiology, baseline characteristics, morphology, clinical presentation, and outcomes. Nevertheless, the underlying mechanisms, contributing factors, and potential solutions to address the disparities compared to men remain poorly understood. Recent research has aimed to identify sex differences in the epidemiology and pathophysiology of AS; however, conflicting findings underscore the necessity for further investigation to clarify these differences and establish precise definitions of severe AS in women. The absence of sex-specific criteria for evaluating AS severity and cardiac flow state may contribute to delayed referral patterns and the unfavorable outcomes often seen in women. Although female patients account for half of those undergoing TAVR in clinical studies, there is a lack of sex-specific subanalyses, and the influence of sex on outcomes has not been thoroughly explored, especially in the long run. Therefore, clinical studies focused specifically on the sex-specific characteristics of AS patients treated with TAVR are essential to tailor treatments to the unique needs of women.

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