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Sex-Specific Considerations in Degenerative Aortic Stenosis for Female-Tailored Transfemoral Aortic Valve Implantation Management

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CONTEMPORARY REVIEW

Sex-Specific Considerations in Degenerative Aortic Stenosis for Female-Tailored Transfemoral Aortic Valve Implantation Management

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ABSTRACT: The impact of sex on pathophysiological processes, clinical presentation, treatment options, as well as outcomes of degenerative aortic stenosis remain poorly understood. Female patients are well represented in transfemoral aortic valve implantation (TAVI) trials and appear to derive favorable outcomes with TAVI. However, higher incidences of major bleeding, vascular complications, and stroke have been reported in women following TAVI. The anatomical characteristics and pathophysiological features of aortic stenosis in women might guide a tailored planning of the percutaneous approach. We highlight whether a sex-based TAVI management strategy might impact on clinical outcomes. This review aimed to evaluate the impact of sex from diagnosis to treatment of degenerative aortic stenosis, discussing the latest evidence on epidemiology, pathophysiology, clinical presentation, therapeutic options, and outcomes. Furthermore, we focused on technical sex-oriented considerations in TAVI including the preprocedural screening, device selection, implantation strategy, and postprocedural management.

Key Words: aortic stenosis ■ clinical management ■ device selection ■ sex differences ■ transcatheter aortic valve implantation

Degenerative aortic stenosis (AS) currently represents one of the most frequent nonrheumatic valvular heart diseases worldwide.[1] Nevertheless, the impact of sex on pathophysiology, clinical presentation, and outcomes in AS remains poorly defined.[2] Female patients are well represented in the transcatheter treatment of severe AS, both in national registries and landmark trials, and several lines of evidence suggest that women might experience greater benefit than men with transfemoral aortic valve implantation (TAVI) compared with surgical treatment.[3–7] In this review, we aimed to describe the impact of female sex on diagnosis and management of severe AS, discussing the latest evidence on epidemiology, pathophysiology, presentation, and treatment. The novelty of this review is its focus on technical sex-oriented considerations ranging from preprocedural screening to periprocedural tricks and postprocedural management, including the latest technological innovations. Moreover, we aimed to report whether sex-based TAVI management protocols might impact on clinical outcomes.

IMPACT OF FEMALE SEX IN THE DIAGNOSIS OF ACQUIRED AS

Epidemiology, Pathophysiology, and Natural History

The prevalence of symptomatic severe AS is up to 4% in elderly patients (aged >75 years), with equal frequency

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Nonstandard Abbreviations and Acronyms

AS	aortic stenosis
MDCT	multidetector computed tomography
TAVI	transfemoral aortic valve implantation
THV	transcatheter heart valve

in men and women and a mortality rate of over 50% at 2 years of follow-up unless promptly treated.[1,8] The main cause of acquired AS involves a degenerative age-related valve mineralization, a dynamic process with lipid accumulation, chronic inflammation, and active valve leaflet calcification. However, little is known about the role of sex in the progression of valve disease and in the ventricular response to the pressure overload (Figure 1). In contrast to men, who develop a fibrotic dilated cardiomyopathy, left ventricular ejection fraction (LVEF) is less likely to deteriorate in women who experience a relatively greater wall thicknesses but smaller left ventricular (LV) cavities because of concentric hypertrophy. This remodeling process reverses more often in women shortly after aortic valve replacement.[9] The pathological explanation for such different remodeling patterns and the extent of ventricular fibrosis partly relies on a lower expression of profibrotic and inflammatory genes (eg, collagen I–II, matrix metalloproteinase 2, transforming growth factor-β signaling pathways), which have been found in the interstitial cells of intraoperative myocardial biopsy specimens.[10] Differences in valve morphology have also been described, because female sex is associated with a lower degree of aortic valve calcification measured by multidetector computed tomography (MDCT) in patients with a similar degree of hemodynamic stenosis severity evaluated at Doppler echocardiography, even after adjustment for body surface area (BSA) and echocardiographic parameters.[9] The histological detection of higher levels of valvular fibrosis and dense connective tissue might explain why in women a more fibrotic aortic valve remodeling is observed for a given aortic stenosis severity. In contrast, male patients have histological evidence of more pronounced calcific valve remodeling irrespective of patients' age.[11–13] Conflicting data exist on the natural progression of AS according to sex. Some data suggest similar progression of aortic valve disease in men and women with respect to the gradient, velocity, or valve area; whereas other studies have reported that female sex is an independent predictor of mean aortic valve gradient progression, showing a significant association with AS-related event rates at long-term follow-up.[14]

Clinical Presentation

The role of sex in the modulation of the pathological processes associated with the development of AS translates into different clinical phenotypes and decision-making strategies (Figure 1).[8,12,15] Almost half of women with severe AS are asymptomatic and therefore diagnosed at later stages, with a lower rate of referral to treatment.[16] As symptoms appear, female patients are older and experience higher rates of symptomatic heart failure with shortness of breath along with dizziness and syncope.[17] The heavier symptomatic burden in the context of a chronic LV pressure overload may be explained by the relative higher LV wall thickness, smaller LV cavity, and LV filling pressures in women.[18] In contrast, men tend to have a higher prevalence of comorbidities, in particular coronary and peripheral artery disease and diabetes; in contrast, female patients show a greater prevalence of chronic kidney disease.[14,17]

Diagnostic Assessment

Consistent sex-specific guideline criteria for the grading of disease severity are still lacking. Echocardiographic assessment warrants indexed values for BSA (aortic valve area index, <0.6 cm^2/m^2), but the same correction has not been applied for other hemodynamic parameters such as mean gradient or peak velocity.[8] Transthoracic echocardiogram evaluation is often challenging, because it may underestimate the LV outflow tract area and stroke volume, resulting in discrepancies between mean gradient and aortic valve area index.[19] In addition, up to 40% of patients present with a severe reduction of calculated aortic valve area index with low-gradient AS. The classical low flow–low gradient because of low LVEF is more prevalent in men, whereas a paradoxical low flow–low gradient disease, where LVEF is preserved but stroke volume index is <35 mL/mq, is more common in elderly women because of their small, restrictive LV cavity, greater arterial stiffness, and higher ventriculo-arterial impedance. This process may be found in 10% to 15% of the AS population and may lead to paradoxical underestimation of the severity of the disease,[20] leading to undertreatment of female patients. Although the transthoracic echocardiogram remains the standard diagnostic test, MDCT could provide more detailed quantification of AS severity and progression, using the true MDCT measured LV outflow tract area for reclassification of aortic valve area and calculation of the aortic valve calcium load that is strongly associated with worse morbidity and mortality.[21,22] Women require lower levels of aortic valve calcium load to reach hemodynamically severe AS compared with men, with sex-specific calcium scores for the diagnosis of AS.[8,14,23] Thresholds for severe AS assessed by means of computed tomography measurement of aortic valve calcification (Agatston units) are: men>3000, women>1600=highly likely; men>2000, women>1200=likely; men<1600, women<800=unlikely. Interestingly, this discordant calcific/fibrotic patterns between men and women may be

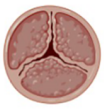
Epidemiology ♀	Prevalence of severe AS	Up to 4% between elderly patients (>75 years) ≅ frequency in men and women
	Natural progression	Conflicting results on disease progression High rate of asymptomatic severe AS but greater symptomatic burden Lower prevalence of comorbidities
Pathophysiology 	Patterns of AV remodeling	↓ extent of AVC load but comparable degree of valvular stenosis ↑ levels of valvular fibrosis and dense connective tissue
	Patterns of LV hypertrophy	↓ extent of ventricular fibrosis (↓ expression of pro-fibrotic and inflammatory genes) ↑ concentric hypertrophy ↑ wall thicknesses and LVEF ↓ LV cavities
Diagnostic assessment 	Echocardiography	LV concentric remodelling ↑ paradoxical LF-LG AS
	MDCT	Smaller anatomic root Lower coronary take off ↓ AVC threshold for severe AS Smaller ileo-femoral vessels and BSA
	cMR	↓ LV mass index ↑ myocardial fibrosis

Figure 1. Epidemiological, pathophysiological, and diagnostic peculiarities in female patients affected by degenerative AS. AS indicates aortic stenosis; AV, aortic valve; AVC, aortic valve calcification; BSA, body surface area; cMR, cardiac magnetic resonance; LF-LG, low flow–low gradient; LV, left ventricular; LVEF, left ventricular ejection fraction; and MDCT, multidetector computed tomography.

exacerbated in specific valve morphology such as stenotic bicuspid valve that shows less aortic valve calcification for the same hemodynamic severity not only in men but also compared with women with severe tricuspid aortic valve stenosis.[13] Lastly, cardiac magnetic resonance could provide complementary information on LV function, because it allows identification of different patterns of hypertrophy and remodeling and quantifies the extent of LV fibrosis in late gadolinium enhancement assessment.[24] However, data on cardiac magnetic resonance evaluation of sex differences in myocardial LV fibrosis are still limited. Nevertheless, the sex differences in the pathophysiological process and clinical presentation of severe AS might further benefit from an integrated diagnostic approach to avoid late referral and adverse outcomes encountered in female patients.

IMPACT OF FEMALE SEX IN THE TREATMENT OF AS

Current Guidelines Recommendations and the Role of the Heart Team

Historically, female patients with AS have been turned down for surgical aortic valve replacement more often than men, mainly because of their late presentation and perceived greater risk of perioperative complications.[25] The introduction of TAVI flattened the sex-related gap in the treatment of AS; women represent >50% of patients undergoing TAVI.[26] Nevertheless, although female sex is a known risk factor for perioperative mortality in both the EuroSCORE and the Society of Thoracic Surgeons risk score, current international guidelines do not provide sex-specific recommendations on treatment.[8,27] The heart team plays a pivotal role in the selection of the optimal modality of intervention (surgical or transcatheter) for each individual patient, based on clinical, anatomical, and procedural features.[8] Factors favoring the choice of TAVI over surgical aortic valve replacement in female patients include advanced age at presentation, greater frailty, lower prevalence of concomitant severe coronary artery disease, and higher likelihood of patient–prosthesis mismatching smaller aortic annulus.[8]

TAVI in Female Patients: Summary of Clinical Outcomes

Current data around TAVI outcomes in female patients compared with male patients are derived from subanalyses of randomized trials and observational studies (Table 1).[4–7,25,28–37]

Among comparative studies, in the combined cohorts of the PARTNER (Placement of Aortic

Table 1. Studies Comparing the Main Clinical Outcomes After Transcatheter Aortic Valve Implantation in Female and Male Patients

Study or first author and design	Overall population, n	% Women	Follow-up	Mean age, y		Operative risk, %		Vascular complications		Bleeding		All-cause mortality	
				Women	Men	Women	Men	Women	Men	Women	Men	Women	Men
FRANCE 2 registry, prospective observational[28]	3972	49.5	1 y	84.0±6.6	81±6.5	21.4±13*	22.2±15.2*	4.6	1.9	4.3	1.9	19.3	23.7
Kodali et al, analysis of RCT[5]	2559	47.6	30 d	84.9±6.9	84.1±7.3	11.9±4.2	11.1±4.0	17.3	5.08	10.5	7.7	6.5	5.9
Szerlip et al, analysis of RCT[4]	1661	39.5	1 y	82.5±7.2	82.0±7.1	6.8±3.0	6.3±2.8	7.2	4.2	16.7	14.6	9.4	10.4
Sannino et al, retrospective observational[29]	910	46.5	1 y	82.0±7.6	80.9±8.4	7.9±3.7	7.1±4.0	7.8	4.1	4.0	1.6	7.0	12.7
Doshi et al, retrospective observational[30]	41 050	47.7	In-hospital	81.7±8.1	80.5±9.1	…	…	3.9	3.3	28.3	20	4.7	3.9
Stehli et al, prospective observational[31]	683	58	30 d	84.2±5.2	83.2±6.9	5.2±3.1	4.6±3.5	8.2	5.6	3.3	1	2.4	0.3
FRAILTY-AV, prospective observational[25]	759	44.8	1 y	84.2±5.3	82.8±5.8	6.5±3.8	5.8±4.4	…	…	…	…	19	17
TVT registry, prospective observational[32]	23652	49.9	1 y	82.3±8.5	81.7±8.6	9±6	8±6	8.3	4.4	8.0	5.9	21.3	24.5
Forrest et al, analysis of RCT[6]	3687	46.3	1 y	84.0±7.6	82.7±7.9	9.6±4.9	8.3±4.6	9.7	4.9	42.7	31.2	21.3	24.1
D'Ascenzo et al, retrospective observational[33]	377	57.2	30 d	82.9±5.4	81.6±5.3	5.6±3.1	7.6±6.2	12.9	9.8	44	25	7.4	8.7
Italian Multicenter CoreValve registry, prospective observational[34]	659	55.8	1 y	82±5	80±7	23±14*	23±14*	2.2	1.7	3.5	2.7	16	19
Humphries et al, analysis of RCT[7]	641	51.3	30 d	83	82	7.5	7.5	12.4	5.4	21.6	15.8	6.5	11.2
Czarnecki et al, retrospective observational[35]	999	45.3	1 y	85	83	7.0±5.0*	8.0±7.0*	18.7	16.7	14.5	12.6	18.2	19.2
Katz et al, prospective observational[36]	819	51	30 d	82.4±7.0	80.6±7.5	15.4±13	11.4±9.5	11.2	5.5	7.4	6.2	11.5	6.5
Tarantini et al, prospective observational[37]	1694	49	30 d	82.7±6.3	80.8±6.9	17.9±11.7*	17.8±13.9*	3.7	2.7	…	…	36†	39.7†

FRAILTY-AVR indicates Frailty Aortic Valve Replacement study; FRANCE 2, FRench Aortic National CoreValve and Edwards 2 registry; RCT, randomized control trial; TAVI, transcatheter aortic valve implantation; and TVT, Transcatheter Valve Therapy registry.

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

†4-year results.

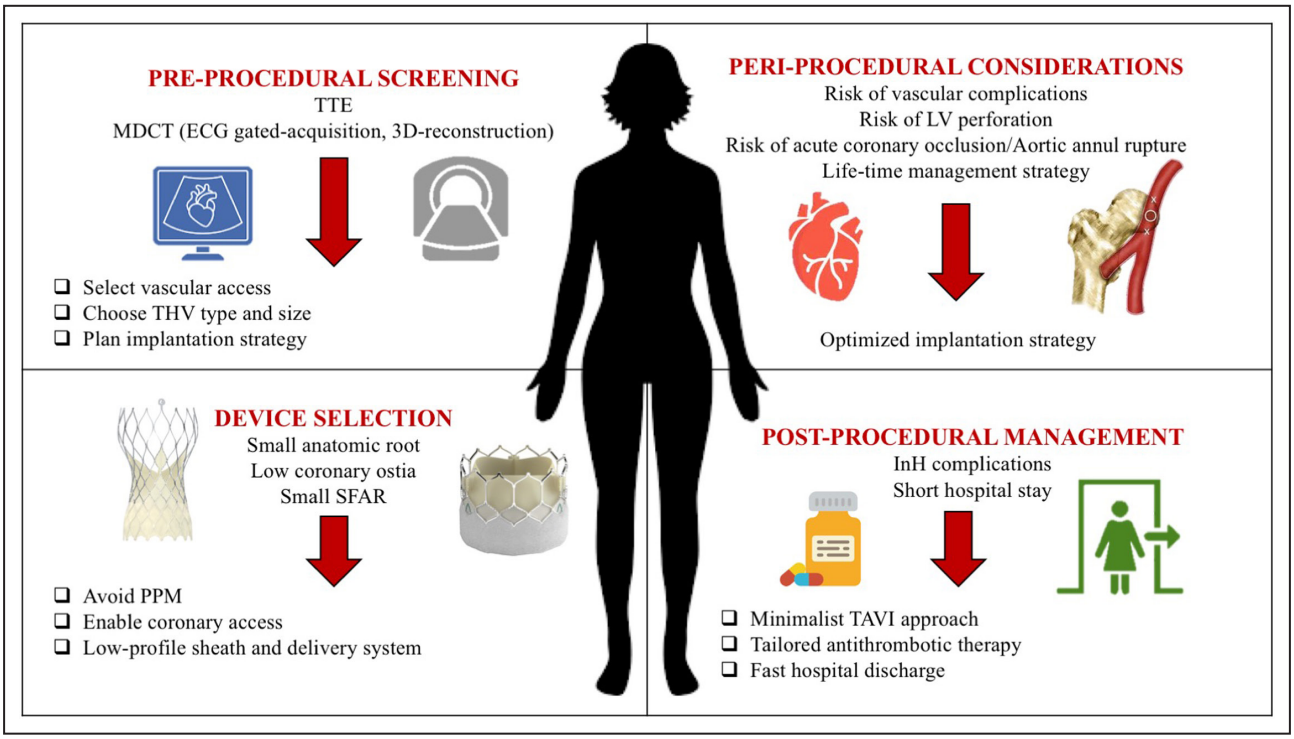


Figure 2. Sex-tailored TAVI planning and periprocedural management.
3D indicates 3 dimensional; InH, in hospital; LV, left ventricular; MDCT, multidetector computed tomography; PPM, prothesis–patient mismatch; SFAR, sheath-to-femoral artery ratio; TAVI, transcatheter aortic valve implantation; THV, transcatheter heart valve; and TTE, transthoracic echocardiogram.

Transcatheter Valves) II SAPIEN 3 (S3) (Edwards Lifesciences) trial, which included high- and intermediate-risk patients, female sex was independently associated with an increased risk of major vascular complications, but no differences in 30-day survival or stroke rate were observed in women compared with men.[4] In the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy registry, vascular complications were more frequent among 11 808 women compared with 11 844 men (8% versus 4%; adjusted hazard ratio [HR], 1.7 [95% CI, 1.3–2.1]; $P<0.001$), whereas mortality at 1 year was lower (21% versus 25%, adjusted HR, 0.7 [95% CI, 0.6–0.9]; $P<0.001$).[32] Likewise, in 2 large meta-analyses, women experienced higher rates of major vascular complications, major bleeding events, and stroke than men.[26,38] A low BSA and smaller peripheral vessel diameter increases the risk of bleeding and vascular complications in the periprocedural phase. In this context, device innovation has the potential to mitigate the burden of access-site complications in women undergoing TAVI through a progressive reduction of the size and profile of delivery systems and the extended use of expandable sheaths.[39] On the other hand, female sex was associated with a survival advantage at long-term follow-up (mean follow-up length of 3.3±1.1 years).[29] A lower prevalence of comorbidities in addition to the longer life expectancy enjoyed by women compared with men in the general population may drive the higher survival reported in the longer term. Conversely, an analysis of a contemporary cohort of patients treated with the SAPIEN 3 (Edwards Lifesciences, Irvine, CA) or Corevalve Evolut R or Evolut Pro (Medtronic, Minneapolis, MN) valves found similar rates of in-hospital mortality, stroke, and pacemaker implantation in women and men.[40]

The WIN TAVI (Women's International Transcatheter Aortic Valve Implantation) registry was the first international, multicenter, prospective observational registry of 1019 female patients undergoing TAVI at 18 European and 1 North American center between 2013 and 2015. Baseline clinical characteristics included a mean age of 83 years and mean LVEF of 56; ≈90% of patients were considered at high risk for surgery. Transfemoral TAVI was performed in 91% of cases, with 42% use of second-generation valves. At 30-days, the primary VARC-2 (Valve Academic Research Consortium 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) occurred in 14% and was mainly driven by vascular complications (7.7%) or bleeding events (4.4%). Increasing age, history of stroke, LVEF <30%,

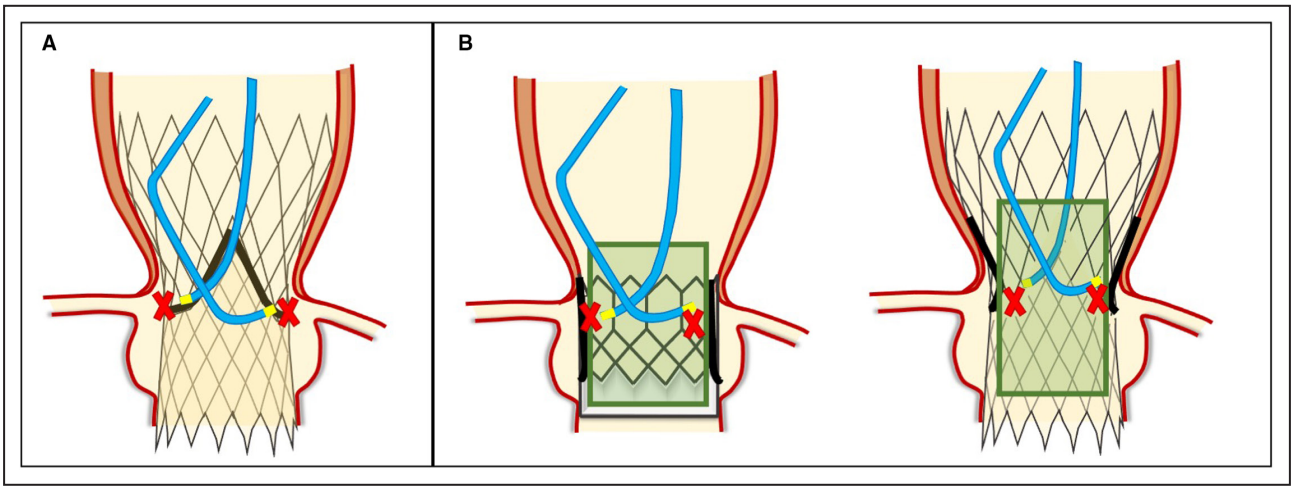


Figure 3. Unfavorable anatomical correlation between THV frame, small aortic root, and coronary ostia, both in native and in bioprosthetic valve TAVI procedures.
A, Possible anatomical relationship between a self-expandable supra-annular device and a small annulus and STJ, that may hamper selective coronary artery cannulation because of a high sealing skirt. **B**, Scenario of a TAVI-in-TAVI procedure in case of a small aortic root with a narrow distance between the THV and STJ (<2 mm). Whatever is the first THV (intra-annular or supra-annular), if its commissural plane is at the level or even above the STJ, the implantation of a second THV may entail the risk of coronary obstruction because of sinus sequestration.[71,72] STJ indicates sinotubular junction; TAVI, transcatheter aortic valve implantation; and THV, transcatheter heart valve.

and first-generation devices were found independent predictors of the primary end point.[41] At 1 year, a primary efficacy composite end point (including mortality, stroke, myocardial infarction, hospitalization for valve-related symptoms or heart failure or valve-related dysfunction) occurred in 167 (16.5%) patients, with nearly half of the rates previously reported in studies including first-generation devices; rates of all-cause mortality and stroke were 13% and 2%, respectively. No associations between history of pregnancy and 1-year outcomes were observed.[42]

Additional evidence is expected with the results of the RHEIA (Randomized Research in Women All Comers With Aortic Stenosis) trial, a prospective, randomized multicenter study that tests noninferiority and, eventually, the superiority of TAVI versus surgical aortic valve replacement for a primary end point composed of all-cause mortality, all stroke, and rehospitalization for valve or procedure-related symptoms or worsening congestive heart failure at 1 year after the procedure among >400 women with severe aortic stenosis (NCT04160130).[43]

PROPOSED SEX-ORIENTED TAVI MANAGEMENT

The distinctive anatomical characteristics and pathophysiological features of AS in women affect outcomes after TAVI and should guide tailored TAVI planning, procedural strategy, and postprocedural management (Figure 2). Several measures and technical tricks can be implemented during standard TAVI planning and the procedure to minimize adverse events in a sex-oriented approach, taking into account the longer life expectancy of female patients. All the proposed recommendations are integrated into a contemporary lean TAVI clinical pathway.[44,45]

Preprocedural Screening and Device Selection

Currently, preprocedural screening of a patient candidate to TAVI is the same for women and men and consists of a multimodality imaging evaluation including transthoracic echocardiography, coronary angiography, MDCT, according to institutional protocols.[46] Among them, the gold standard imaging modality is MDCT, which can also play a role in screening for coronary artery disease.[47] As previously highlighted, women present more often with a small anatomic root (including small annulus, sinus of Valsalva, and sinotubular junction), low coronary ostia, and small iliofemoral vessels resulting in an unfavorable sheath-to-femoral artery ratio, together with a small BSA.[48,49] Accordingly, careful measurement of these parameters should be performed and compared with the anatomical requirements for the different available transcatheter heart valves (THVs) and their respective sizing charts to select the most appropriate THVs and vascular access in a patient-tailored fashion.[50]

First of all, it is well noted that currently available THVs cover different specific ranges of annulus size, with SAPIEN (Edwards Lifesciences), Corevalve Evolut

(Medtronic), Portico (Abbott Structural Heart, Santa Clara, CA), Allegra (New Valve Technology, Hechingen, Germany), and Myval (Meril Life Sciences, Gujarat, India) as those who are approved for the small annulus size (<20 mm). To date, there are no randomized trial data with regard to the superiority of one device to others in the case of a small annulus size. The SMART (Small Annuli Randomized to Evolut or SAPIEN) trial, comparing the 2 most widely available contemporary TAVI devices, the Medtronic Evolut PRO/PRO+ self-expanding and the Edwards SAPIEN 3/SAPIEN 3 Ultra balloon-expandable devices in aortic valve annulus area of ≤430 mm^2, is still ongoing.[51] The SMART trial will be the largest trial to enroll primarily female patients.

Second, the presence of small annulus size (generally considered as an annulus size <23 mm), one of the predictors of patient–prosthesis mismatch even after THV implantation, should be taken into account for device selection.[52,53] Patient–prosthesis mismatch after TAVI may be associated with less regression of LV hypertrophy, LV diastolic dysfunction, LV filling pressure, less improvement in LV systolic function, and less reduction of left atrial volume.[54] However, clinical data to demonstrate the impact of patient–prosthesis mismatch on long-term outcomes after TAVI are not available yet.[52,55] In practice, one may argue that, in case of a small annulus size, it is worthwhile to pursue the largest effective orifice area and the lowest transvalvular gradient through the use of a self-expandable supra-annular device. However, the sealing skirts of supra-annular devices are particularly high, and especially in the case of associated small sinotubular junction, may hamper selective coronary artery cannulation (Figure 3).[56–58]

Finally, the delivery sheath profile must be obviously considered in the choice of the most appropriate THV. As discussed above, in case of suboptimal vascular access (small sheath-to-femoral artery ratio, higher tortuosity, and diffuse and circumferential calcification), a device with a low-profile delivery system has to be selected. The CoreValve Evolut R and Pro+ (Medtronic) can be implanted using the InLine sheath with 14 Fr outer diameter equivalent (minimum vessel diameter requirements, 5.0 mm for sizes 23, 26, 29 mm, in the absence of circumferential calcification); also, the last generation low-profile delivery system FlexNav (Abbott Structural Heart, Santa Clara, CA) designed for the Portico and Navitor valve (Abbott Structural Heart), provides the same low insertion profile (access down to 5.0-mm vessels). Other devices require at least 5.5 mm minimum vessel diameter or larger. If transfemoral access is not feasible, the heart team can consider different peripheral vascular approaches such as transubclavian/transaxillary (both CoreValve and Portico iterations have a Conformitè Europëenne mark of approval for this vascular approach).

Implantation Strategy and Periprocedural Considerations in Female Patients

Risk of Vascular and Access-Related Complications

Because female sex seems to be independently associated with an almost double risk of vascular complications after TAVI, with a relative risk of 1.6 compared with men,[26] it is mandatory to adopt every possible technique to minimize this risk as per Figure 4:

1. Use of 2-dimensional ultrasound guidance during access site vascular puncture, because it has been associated with a significant reduction in the rate of major vascular complications and major bleeding over conventional fluoroscopic guidance.[59]
2. In case of heavy, circumferential calcifications, additional tools should help to increase patient eligibility and reduce vascular complications (ie, percutaneous transluminal angioplasty, paving and cracking endovascular techniques, debulking devices). Among them, intravascular lithotripsy is a recent promising technique in which ultrasound disrupts intimal and medial calcification, altering vessel compliance to allow for the safe passage of large-bore delivery sheaths.[60] This expands the patient cohort that could be eligible for transfemoral access, which still remains the first choice whenever possible and is associated with decreased morbidity and mortality compared with nontransfemoral access.[61] However, alternative routes may be considered (transubclavian, transcarotid, transapical, transaortic, transcaval) in case of an unfeasible transfemoral route.
3. A minimalistic approach with a radial access to guide valve implantation or manage peripheral vascular complications and an over-the-wire rapid pacing reduce the secondary access site failures.[62,63] In case the secondary artery access is the contralateral femoral artery, the prepositioning of a crossover guidewire may help in the management of any vascular complication should it occur.
4. The hemostasis technique is of outmost importance. A balloon inflation advanced from contralateral femoral artery to create a dry field during final hemostasis may be helpful for managing TAVI vascular access sites.[64] Most importantly, different sutured-based and collagen plug-based vascular closure devices are now available. The use of 2 Perclose Proglide (Abbott Vascular, Santa Clara, CA) devices was associated with a lower rate of major or minor vascular complications and lower rates of acute kidney injury in patients undergoing transfemoral TAVI in comparison to Prostar XL (Abbott Vascular).[65] Moreover, the plug-based Manta device (Teleflex, Wayne, PA), specifically designed for large-bore arteriotomy closure, recently showed reliable safety and

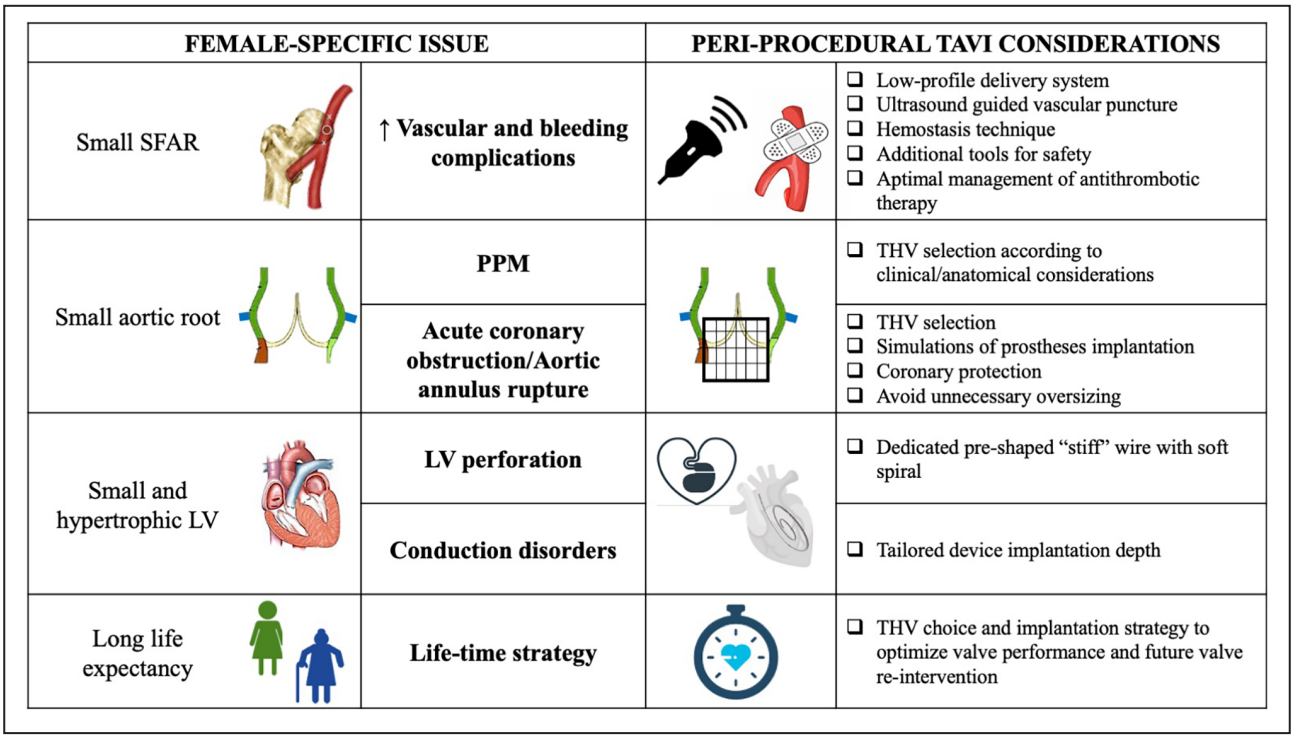


Figure 4. Periprocedural TAVI considerations to address the specific issues associated with the treatment of female patients.
LV indicates left ventricle; PPM, patient–prosthesis mismatch; SFAR, sheath-to-femoral artery ratio; TAVI, transcatheter aortic valve implantation; and THV, transcatheter heart valve.

efficacy in selected TAVI populations. Further registry data suggested that it was associated with faster hemostasis and a lower rate of vascular complications compared with the suture-based strategy, whereas early randomized studies highlighted a higher than anticipated rate of Manta-access vascular events (up to 19%).[66,67] It remains to be determined whether inherent differences in the design and operation of those devices may guide a sex-tailored choice.

5. The optimal management of antithrombotic therapy during the periprocedural phase may significantly impact on the rate of vascular complications. In particular, considering the frequent low body weight of female patients, it is recommended to administer a weight-based dose of unfractioned heparin with a close monitoring of activated clotting time. In line with the most recent scientific evidence and recommendations, dual antiplatelet therapy should be administered only in case of recent percutaneous coronary intervention.[68]

Risk of Left Ventricle Perforation

A small left ventricle cavity and an hypercontractile state, frequently encountered in female patients with AS, together with a thin muscular wall and a narrow aorto-mitral angle, are potential predictors of the occurrence of left ventricle perforation during TAVI.[69] Left ventricle perforation primarily occurs secondary to the valve delivery wire inadvertently being pushed too distally through the left ventricle apex in a small cavity, even if the operators perform an appropriate curve on the distal stiff end of the wire.

It is suggested to use dedicated preshaped stiff wires with soft spiral tips to mitigate this risk. For example, the Amplatz Extra-Stiff APEX wire (Cook Medical) has a double curve design composed of a larger curve with the distal tip of the wire forming a 2-mm J bend; it can be easily maneuvered in smaller ventricles, whereas the Safari2TM wire is available in 3 different loop sizes, offering the possibility to select the curve size according to the size of the ventricle[70] (Figure 4).

Risk of Acute Coronary Occlusion

Female sex is one of the strongest baseline clinical factors associated with the risk of acute post-TAVI coronary occlusion, a rare but life-threatening complication; in several observational experiences focusing on coronary obstruction following TAVI, the vast majority (>80%) of patients were women.[71] Coronary obstruction following TAVI is mainly caused by the displacement of the calcified native leaflet over the coronary ostia in the presence of lower coronary ostia and/or narrow aortic root, leaving little room to accommodate the native aortic leaflets, and as previously

described, these are frequent anatomical features in female patients.[48] Moreover, in patients with prior surgical or percutaneous aortic valve treatment undergoing valve-in-valve or TAVI-in-TAVI procedures, the risk of acute coronary occlusion, either directly or indirectly by sequestering the sinus of Valsalva at the sinotubular junction, is up to 6-fold higher compared with TAVI for native aortic valve disease.[72] Many criteria for selecting patients at high risk for obstruction have been proposed, including 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, respectively, of ≤4 and ≤2 mm, degenerative stentless bioprosthetic valve, or with externally mounted leaflets.[73]

Along with a tailored THV choice considering future valve reintervention in a lifetime management strategy, several periprocedural measures are useful to mitigate the risk of acute coronary obstruction, such as (Figure 3 and 4):

1. Accurate MDCT preprocedural planning with virtual simulations of prostheses implantation (the usefulness of 3-dimensional printing models is under investigation in this field).
2. If pre-TAVI balloon valvuloplasty is required, simultaneous angiography to depict coronary patency or obstruction.
3. In case of the abovementioned clinical and anatomical parameters of risk, consider leaflet modification strategies (ie, BASILICA [Bioprosthetic or Native Aortic Scallop Intentional Laceration to Prevent Iatrogenic Coronary Artery Obstruction]) and/or different technical strategies for coronary patency protection (eg, guiding catheter placement, guidewire placement, prepositioned stent, ready to be deployed after TAVI in a chimney or snorkel fashion, or orthotopic stent strategy).[73]
4. Use of self-expandable valves with a concave shape nitinol frame at the level of coronary arteries (with mandatory commissural alignment during implantation) rather than a balloon expandable straight cobalto-chromium frame.[71]
5. Use of a repositionable/retrievable THV or a valve with different anchoring mechanism (paper clip–like anchorage mechanism at the level of the leaflets).[74]
6. Avoid unnecessary oversizing.

Risk of Paravalvular Leak and Aortic Annulus Rupture

Again, in a small hypertrophic left ventricle, any pressure or volume residual overload can impact on symptoms relief and clinical outcome. Notwithstanding, female patients less frequently experience residual paravalvular leak; smaller annular size, greater use of TAVI oversizing, lower aortic valve calcification burden, and higher achieved true cover index typically found in female patients undergoing TAVI are likely contributing factors to this finding.[75] Conversely, balloon-expandable TAVI oversizing ≥20% of the annular area is associated with an 8-fold increased risk of annulus rupture, and this is more frequently described in women than men.[76]

1. It is generally recommended to optimize the procedural result by an accurate evaluation of valve hemodynamics in the catheterization laboratory (residual gradients and regurgitation). It is advisable to assess invasively any residual transprosthetic gradient.
2. Intra- or paravalvular leak has to be accurately detected by multimodality evaluation (including supraortic angiogram, intraprocedural echocardiogram evaluation, aortic and left ventricle invasive pressure measurements, aortic regurgitation index) to try to optimize the result by means of adjunctive maneuvers (ie, after dilatation).[77] The use of the dicrotic notch index to assess for paravalvular leak avoiding left ventricle measurements is currently under investigation.[44]

Risk of Conduction Disorders and Permanent Pacemaker

A left bundle-branch block and the dyssynchrony lead by pacing stimulation are badly tolerated in case of a small hypertrophic left ventricle.

1. A valve implant as high as possible may help to reduce the risk of conduction disorders[78] (Figure 4).
2. If a pacemaker is needed, the most physiological stimulation modality should be pursued, and atrial contribution should be preserved whenever possible. Within this perspective, the measurement of membranous septum length by computed tomography scan can provide a patient-specific approach to device implantation depth, because implanting the device at a depth less than the membranous septum length helps to significantly reduce permanent pacemaker rate.[79]

Lifetime Management Strategy

Considering the longer life expectancy of women, it is particularly advisable to tailor THV choice and implantation strategy to optimize valve performance and foresee the strategy of future valve reintervention[80] (Figure 4). Different scenarios may arise:

1. In the case of a small sinus of Valsalva and narrow sinotubular junction, the priority should be

to preserve the easiest coronary reaccess possible, with consideration of future valve-in-valve. Accordingly, in case of short-frame THV device selection, a slightly deeper implantation into the LV outflow tract can be attempted (for example, 60:40 instead of 70:30 or 80:20) to keep the neocommissural plane below the coronary ostia plane. On the other hand, if a long-frame device is implanted, implantation strategies aiming to obtain commissural alignment should be implemented.[81]
2. In case of elderly patients with a larger BSA, a supra-annular device may be a good option, particularly when using commissural alignment strategies during implantation. On the other hand, in patients with known associated coronary artery disease and/or longer life expectancy (entailing an increased risk of further procedures of TAVI-in-TAVI or percutaneous coronary intervention), a balloon expandable intra-annular short frame device could be preferred, especially if implanted in a subcoronary position.[82–84]

The enrolling SMART trial may help to address this issue.[51]

POSTPROCEDURAL MANAGEMENT

Contemporary TAVI programs have to streamline postprocedural care and discharge policy, with no distinction between sexes.[44,45] However, in light of the greater simplification of the TAVI procedure and shortened length of hospital stays, specific attention should be paid to the risk of complications as well as to a tailored pharmacotherapy in female patients.

The increasing clinical experience and advances in device technology have led in many centers to a paradigm shift from general anesthesia to local anesthesia or conscious sedation followed by early discharge (within 48 hours), irrespective of surgical risk.[85,86] Recent observational data support the benefit of a minimalist approach with reduced procedure time and shorter hospitalization, where next-day discharge will become standard practice, resulting in cost-effective quality care.[44,45] A reduced risk of nosocomial infections and increased chance of being discharged home is highly appealing in women who are generally older, with less comorbidities, and present later in their disease trajectory to TAVI services.[15,87]

Notwithstanding, the length of hospitalization after a TAVI procedure is a delicate balance between benefit of early discharge and timely detection of postprocedural complications and should be tailored to individual patient's medical needs. Advanced age, low BSA, and small vessels make women at higher risk for bleeding and vascular complications in the early period after the procedure. However, careful access-site monitoring and serial hemoglobin measurements within 48 hours allow identification of the majority of vascular access site-related complications before discharge. The FAST TAVI (Feasibility and Safety of Early Discharge After Transfemoral Transcatheter Aortic Valve Implantation) registry demonstrated that prespecified risk criteria based on the rate of 30-day complications could identify patients (48% women) for whom early discharge was safe and effective.[88] Among others, stable hemoglobin values and preserved renal function are pivotal risk evaluation criteria for early discharge and should be attentively examined in women who may have greater prevalence of chronic kidney disease and anemia.[17,89]

The optimal periprocedural antithrombotic regimen to prevent thrombotic complications and minimize the risk of bleeding is also important.[90–93] Several randomized trials have investigated the safety and efficacy of different antithrombotic regimens after TAVI (Table 2). However, no specific recommendations have been indicated for women undergoing TAVI procedures. European guidelines currently recommend life-long single antiplatelet therapy or oral anticoagulation in case of patients who have other indications for oral anticoagulation (antiplatelet therapy); dual antiplatelet therapy should be administered only in cases of recent percutaneous coronary intervention.[8,68,93,94] Female sex representation in major randomized trials investigating antithrombotic therapies after TAVI is almost 50% on average; however, no sex-specific subanalyses have been reported to date (Table 2).[95–101] Observational studies described sex disparities in antiplatelet and antithrombotic management after TAVI with a higher adoption of clopidogrel and a lower use of warfarin because of lower rates of atrial fibrillation.[40] Two large meta-analyses, investigating TAVI outcomes by sex, reported higher rates of major bleeding, vascular complications, and stroke in women, with no impact on survival.[26,40] Moreover, female sex is an independent predictor of anemia in patients with severe aortic stenosis. The WIN TAVI registry showed that not only is anemia a common finding in elderly women, but also strongly correlates to the long-term prognosis.[42] The sex-based assessment of complications and of pharmacokinetic and pharmacodynamic responses to antithrombotic medications are essential in the periprocedural management of women undergoing TAVI. In case of oral anticoagulation therapy, particular attention has to be paid to hemoglobin values, and an accurate reevaluation of the thrombotic and bleeding risks might be suggested during follow-up. More evidence in the context of large clinical trials investigating the safety and efficacy balance of different antithrombotic strategies according to sex are needed to guide therapeutic decision making in daily clinical practice.

Table 2. Overview of Randomized Trials Investigating Antithrombotic Therapies After TAVI

Study	Design	n	Women,%	Treatment strategy	Main findings
Ussia et al[95]	Single-center RCT	79	54.0	3mo DAPT (ASA+C) followed by ASA alone vs ASA	No difference between DAPT vs ASA at 30d (13% vs 15%; *P*=0.71) and 6mo (18% vs 15%; *P*=0.85) in composite of death, MI, stroke, life-threatening bleeding, or urgent conversion to surgery.
ARTE[96]	Multicenter RCT	222	36.9	3mo DAPT (ASA+C) vs ASA	The composite of death, MI, stroke or transient ischemic attack, or major or life-threatening bleeding tended to occur more frequently in the DAPT group (15.3% vs 7.2%, *P*=0.065) within 3mo after TAVI.
POPULAR TAVI (Cohort A)[97]	Multicenter RCT	665	48.7	3mo DAPT (ASA+C) followed by ASA alone vs ASA	12mo all bleeding: 15.1% with ASA vs 26.6% with DAPT (RR, 0.57 [95% CI, 0.42 to 0.77]; *P*=0.001); 12mo composite of death from cardiovascular causes, non–procedure-related bleeding, stroke, or MI: 23.0% with ASA vs 31.1% with DAPT (difference, −8.2 percentage points [95% CI for noninferiority, −14.9 to −1.5]; *P*<0.001; RR, 0.74 [95% CI for superiority, 0.57 to 0.95]; *P*=0.04).
POPULAR TAVI (Cohort B)[98]	Multicenter RCT	313	45.4	3mo OAC+C followed by OAC alone vs OAC	12m all bleeding: 21.7% with OAC vs 34.6% with OAC+C (RR, 0.63 [95% CI, 0.43 to 0.90]; *P*=0.01); 12mo composite of death from cardiovascular causes, non–procedure-related bleeding, stroke, or MI: 31.2% with OAC vs 45.5% with OAC+C (difference, −14.3 percentage points [95% CI for noninferiority, −25.0 to −3.6]; RR, 0.69 [95% CI for superiority, 0.51 to 0.92]).
GALILEO[99]	Multicenter RCT	1644	49.5	3mo rivaroxaban 10mg/d+ASA vs 3mo DAPT (ASA+C)	Primary efficacy outcome composite of death or TE: 9.8 with rivaroxaban and 7.2 with DAPT per 100 person-years (HR, 1.35 [95% CI, 1.01 to 1.81]; *P*=0.04). Primary safety outcome composite of major disabling or life-threatening bleeding: 4.3 with rivaroxaban and 2.8 with DAPT per 100 person-years (HR, 1.50 [95% CI, 0.95 to 2.37]; *P*=0.08).
ENVISAGE TAVI AF[100]	Multicenter RCT	1426	47.5	Edoxaban 60mg/d±antiplatelet therapy vs VKA±antiplatelet therapy	Primary efficacy outcome composite of death from any cause, MI, ischemic stroke, TE, valve thrombosis, or major bleeding: 17.3 with edoxaban and 16.5 with VKA per 100 person-years (HR, 1.05 [95% CI, 0.85 to 1.31]; *P*=0.01 for noninferiority). Major bleeding: 9.7 with edoxaban and 7.0 with VKA per 100 person-years (HR, 1.40 [95% CI, 1.03 to 1.91]; *P*=0.93 for noninferiority)
ATLANTIS[101]	Multicenter RCT	1510	53.0	Apixaban 5mg BID vs single/dual APT or VKA	Primary outcome, time to death, stroke, MI, systemic emboli, intracardiac or valve thrombosis, deep vein thrombosis/pulmonary embolism, or major bleeding for apixaban vs standard of care: 18.4% vs 20.1% (HR, 0.92 [95% CI, 0.73 to 1.16]) (stratum 1: apixaban vs VKA: 21.9% vs 21.9%, stratum 2: 16.9% vs 19.3%; *P* for interaction=0.57). Primary safety end point of life-threatening, disabling, or major bleeding 8.5% vs 8.5%.

APT indicates antiplatelet therapy; ARTE, Aspirin vs Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation; ASA, aspirin; ATLATIS, Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis; C, clopidogrel; DAPT, dual antiplatelet therapy; ENVISAGE-TAVI AF, Edoxaban vs Standard of Care and Their Effects on Clinical Outcomes in Patients Having Undergone Transcatheter Aortic Valve Implantation–Atrial Fibrillation; GALILEO, Global Study Comparing a Rivaroxaban-based Antithrombotic Strategy to an Antiplatelet-based Strategy after Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes; HR, hazard ratio; MI, myocardial infarction; OAC, oral anticoagulant; POPULAR TAVI, Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic-Valve Implantation; RCT, randomized controlled trial; RR, risk ratio; TAVI, transcatheter aortic valve implantation; TE, thromboembolic events; and VKA, vitamin K antagonist.

CONCLUSIONS

Female patients represent half of the patients undergoing TAVI in clinical studies; however, sex subanalyses are limited, and the impact of sex on outcomes has been poorly investigated. Currently, the unique anatomical characteristics and pathophysiological features of AS in female patients should guide tailored TAVI planning and periprocedural management. Further prospective studies focused around optimization of the therapeutic management of women with severe AS are warranted.

ARTICLE INFORMATION

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