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Clinical Outcomes and Imaging Findings in Women Undergoing TAVR

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ABSTRACT

Transcatheter aortic valve replacement (TAVR) has become the standard of care for patients with hemodynamically severe aortic stenosis who are symptomatic but deemed too high risk for surgery. Recent reports suggest that sex differences exist in outcomes following TAVR and in the diagnostic imaging evaluation of patients being considered for TAVR. In this review, the authors explore the differences between men and women in baseline characteristics and outcomes following TAVR, as well as sex differences in the imaging findings of severe aortic stenosis (AS) including the diagnostic challenges in the hemodynamic assessment of severe AS in elderly women, differences in aortic valvular calcification and in the associated myocardial response to severe AS. Additionally, sex differences in imaging findings as they relate to post-TAVR complications including coronary obstruction, annular rupture and prosthesis-patient mismatch are also discussed. (J Am Coll Cardiol Img 2016;9:483–93) © 2016 by the American College of Cardiology Foundation.

With a reported prevalence of 12.4% among elderly patients, aortic stenosis (AS) is considered the most common form of valvular heart disease in ageing Western populations (1). The prognosis of hemodynamically severe and symptomatic AS is poor without valve replacement (2–4). Many elderly patients, however, are considered inoperable due to the prohibitive operative risks associated with multiple comorbidities, which are frequently observed in this population. In this setting, transcatheter aortic valve replacement (TAVR) represents what may be now considered standard care, with randomized trials demonstrating improved clinical outcomes compared with standard therapy in patients considered too high risk for surgery (3), and similar (5) or possibly improved (6) outcomes compared with surgery in high-risk surgical candidates.

Procedural refinement in the last 5 years has led to further improvements in clinical outcomes following TAVR. This has largely arisen through advancement of transcatheter heart valve (THV) technologies and delivery systems; but also as a result of the integration of advanced cardiac imaging into the periprocedural evaluation of TAVR patients. Both multidetector computed tomography (MDCT) and 3-dimensional echocardiography have played critical roles in this regard (7–9). Importantly, however, despite a broad integration of advanced imaging in TAVR, the relative outcomes in men and women remain different as suggested by recent meta-analyses that show a medium-term survival advantage for women following TAVR despite higher rates of short-term complications, particularly major vascular complications (10–12). Moreover, the diagnostic imaging features of patients with severe AS presenting for TAVR; the left ventricular (LV) remodeling in response to severe AS and reverse remodeling following TAVR are different in women compared with men. Accordingly, an imaging-based evaluation of women with severe AS being considered for TAVR should take into consideration these sex-specific differences in presentation and outcomes.

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ABBREVIATIONS AND ACRONYMS

AS = aortic stenosis

AVA = aortic valve area

AVC = aortic valve calcium

CMR = cardiac magnetic resonance

LGE = late gadolinium enhancement

LV = left ventricular

LVOT = left ventricular outflow tract

MDCT = multidetector computed tomography

PLFLG = paradoxical low-flow, low-gradient

PPM = patient-prosthesis mismatch

PVR = paravalvular regurgitation

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

ViV = valve in valve

We review herein the comparative differences in: 1) baseline characteristics and outcomes following TAVR in women; 2) imaging findings of severe AS and the associated myocardial response to severe AS in women presenting for TAVR; and 3) imaging findings as they relate to post-TAVR complications that are more common in women.

BASELINE CLINICAL PROFILE AND CLINICAL OUTCOMES FOLLOWING TAVR IN WOMEN

Although most clinical TAVR studies have collectively analyzed data from both sexes, the baseline clinical risk profile and subsequent clinical outcomes following TAVR are clearly different in women compared with men. Although many studies have shown similar pre-procedural risk between women and men (13-20), recent large meta-analyses demonstrate that overall pre-operative risk stratification scores (logistic EuroSCORE) are lower in women presenting for TAVR compared with men (10,11). In the meta-analysis reported by O'Connor et al. (10), which included patient-level data obtained from 11,310 patients (51% female) in 5 registries, including the PARTNER (Placement of Aortic Transcatheter Valve) trial, the Logistic EuroSCORE was 22.2 ± 13.9 in women and 23.9 ± 15.4 in men ($p < 0.001$) despite the fact that sex is a score component by which female sex adds to overall risk. Women presenting for TAVR generally have a lower burden of overall cardiovascular risk factors and atherosclerotic burden, with lower rates of prior myocardial infarction and revascularization, as well as lower rates of previous stroke and peripheral vascular disease, and better LV systolic function at presentation (10). Similar findings have been shown in other sex-based analyses of TAVR patients (11,15-18,20,21). The prevalence of noncardiovascular comorbidities also appears to be different between sexes, with less pulmonary disease, but more renal insufficiency, reported in women compared with men (10,14,15,19).

Several single and multicenter studies, as well as 3 meta-analyses, have specifically evaluated sex differences in medium-term survival following TAVR (**Table 1**) (10-12). Although some single and multicenter studies showed similar survival between the sexes (14,15,20,22,23), large meta-analyses consistently demonstrate improved medium-term survival following TAVR in women (**Figure 1**) (10-12). O'Connor et al. (10) showed that female sex was independently associated with improved survival at a median follow-up of 387 days, despite higher rates of immediate post-procedural complications, including vascular complications, major bleeding, stroke, and cardiac tamponade. Similarly, Conrotto et al. (11). conducted a meta-analysis that included 6,645 patients (50% female) and also demonstrated a lower mortality rate in women compared with men (24% vs. 34%) at a median follow-up of 365 days, again, despite a higher rate of vascular complications and major bleeding. Stangl et al. (12) also showed 30% lower risk of death in women compared with men at medium term follow-up (> 3 months) despite more frequent major vascular complications in a meta-analysis including data from 7,973 patients (53% female). In addition to the aforementioned sex-specific analyses, in a recent risk-adjusted analysis of mortality using data from the Society of Thoracic Surgeons/American College of Cardiology TVT (Transcatheter Valve Therapies) registry, which included more than 12,000 patients (52% female), female sex was associated with improved survival (24). Similarly, in a propensity-matched analysis of TAVR compared with surgery, female sex was the only predictor of improved survival with TAVR on subgroup analysis (25). This survival advantage with TAVR versus surgery was also shown for women considered high-risk surgical candidates in a retrospective analysis of the PARTNER trial, particularly among women considered suitable candidates for transfemoral access (26).

The improved survival among women undergoing TAVR is in keeping with their lower baseline risk profile and longer mean life expectancy. In addition, the incidence of moderate or greater paravalvular regurgitation (PVR), an important determinant of prognosis post-TAVR (27,28), appears to also be less frequent in women (10,11,18). This may offset the negative mortality impact of other complications, particularly major vascular complications and bleeding, which occur more frequently in women. The determinants of survival post-TAVR may also be different between the sexes. For example, LV systolic dysfunction has been shown to be predictive of mortality in both men and women; however, coronary artery disease is only predictive of death in women, but not in men (17).

Frailty is also an important determinant of mortality post-TAVR; however, there are limited data regarding sex differences at baseline, with mixed results previously reported. In some studies, there was no difference in baseline frailty (19,29,30), whereas women were reportedly more frail than men in another study (13). Importantly, frailty has been shown to be predictive of mortality following TAVR,

TABLE 1 Meta-Analyses Evaluating Sex Differences in Outcomes Following TAVR*

Authors Journal [Year] (Ref. #)	Original Studies Included [Year] (Ref. #)	Total No. (% Female)	Complications	Mortality Risk 30-Day	Mortality Risk Follow-Up
O'Connor et al. J Am Coll Cardiol [2015] (10)	Humphries et al. [2012] (13) Al-Lamee et al. [2014] (22) Gilard et al. [2012] (82) Tamburino et al. [2011] (83) Kodali et al. [2012] (27)	11,310 (51% female)	Favors women: Moderate-severe PVR (19.4% vs.24.5%) Prosthesis-patient mismatch (15.3% vs. 11.9%) Favors men: Major vascular complications (6.3% vs. 3.4%) Major bleeding (10.5% vs 8.5%) Stroke (4.4% vs. 3.6%) Cardiac tamponade (1.3% vs. 0.7%)	No difference (6.5% women vs. 6.5% men)	Favors women Median follow-up 387 days 1-yr survival estimate 82.7% women and 78.2% men Adjusted HR (female sex): 0.79, 95% CI: 0.72, 0.87.
Conrotto et al. Ann Thorac Surg [2015] (11)	Hayashida et al. [2012] (77) Humphries et al. [2012] (13) Zahn et al. [2013] (84) D'Ascenzo et al. [2013] (14) Kirtane et al. [2013] (85)	6,645 (50% female)	Favors women: Moderate-severe PVR (3.1% vs. 5.4%) Favors men: Major bleeding (21.0% vs. 13.0%) Major vascular complications (12.0% vs. 7.4%) No difference: Stroke (2.0% women vs. 2.3% men)	No difference (borderline) (7.0% women and 10.0% men)	Favors women Median follow-up 365 days (365 to 730 days) 24.0% women; 34.0% men Adjusted OR (female sex): 0.82, 95% CI: 0.73–0.93.
Stangl et al. J Interv Cardiol [2014] (12)	Buchanan et al. [2011] (15) Hayashida et al. [2012] (77) Humphries et al. [2012] (13) Stangl et al. [2012] (20) Buja et al. [2013] (16) D'Ascenzo et al. [2013] (14) Onorati et al. [2013] (19) Finkelstein et al. [2013] (86) Al-Lamee et al. [2014] (22) Diemert et al. [2013] (23) Erez et al. [2014] (17) Ferrante et al. [2014] (18) Williams et al. [2014] (26) Sherif et al. [2014] (21)	7,973 (53% female)	Favors women: None Favors men: Major vascular complications (OR: 1.72 [95% CI: 1.41–2.09]) No difference: Stroke (OR: 1.12 [95% CI: 0.85–1.48]) Major bleeding (OR: 1.13 [95% CI: 0.95–1.33])	Favors women (5.9% women vs. 7.5% men)	Favors women >3 months (range: 3 months to 2 yrs minimum) 19.7% women; 25.9% men Unadjusted OR (female sex): 0.70, 95% CI: 0.59–0.82.

*Absolute event rates in parenthesis are presented as women versus men.
CI = confidence interval; HR = hazard ratio; OR = odds ratio; PVR = paravalvular regurgitation; TAVR = transcatheter aortic valve replacement.

independent of sex (13,29). Future studies are needed, however, to better define the interaction among frailty, sex, and mortality following TAVR.

ECHOCARDIOGRAPHIC EVALUATION OF HEMODYNAMICS IN WOMEN WITH SEVERE AS AND SEX DIFFERENCES AMONG PATIENTS PRESENTING FOR TAVR

The echocardiographic diagnosis of AS may pose challenges in elderly women, with more frequent discordance observed in the echocardiographic grading of AS severity based on aortic valve area (AVA) and transvalvular gradient (AVA <1.0 cm^2, but peak aortic velocity <4 m/s and mean gradient <40 mm Hg). This occurs primarily for 2 reasons: 1) women are more predisposed to developing paradoxical low-flow, low-gradient (PLFLG) severe AS due to more concentric LV remodeling that results in a smaller cavity size, restricted LV filling, and therefore, reduced stroke volume; and 2) in the setting of normal stroke volume, women may have a reduced AVA calculated by the continuity principle (due to their smaller LV outflow tract [LVOT] dimensions) despite a nonsignificantly elevated transvalvular gradient and/or nonsignificantly reduced dimensionless index.

Michelena et al. (31) studied the impact of LVOT diameter on inconsistencies in AS severity grading in 9,488 patients with normal LV ejection fraction using echocardiography. Importantly, the majority (91%) of patients with a small LVOT diameter were older women. LVOT diameter contributed significantly to discordance in AS assessment with the guideline AVA cutoff for severe AS of 1 cm^2 (32,33) corresponding to a lower mean and peak transvalvular gradient and lower dimensionless index in patients with a small LVOT diameter compared with patients with an average or large LVOT diameter. Discordant severe AS was observed in 48% of patients with a small LVOT diameter (compared with 37% in average LVOT diameter and 16% in large LVOT diameter). Use of AVA index <0.6 cm^2/m^2 did not significantly change severe AS discordance in the patients with small LVOT diameter. Interestingly, they found that for the small LVOT diameter group, a reduction in the AVA cutoff to 0.8 cm^2 substantially diminished the rate of discordant grading from 48% to 26% of patients. Importantly, however, they noted that such modifications of AVA cutoffs only apply to patients with normal LV stroke volume index (>35 ml/m^2), given that discordance in AS grading may be due to PLFLG severe AS in the presence of a normal ejection fraction. In their study, removing patients with reduced stroke volume (<35 ml/m^2) only partially explained discordance across the groups.

The state of PLFLG is relevant in this setting because elderly women comprise a significant proportion of those presenting with this condition (31,34). Hachicha et al. (34) retrospectively studied a series of 331 patients with severe AS and preserved LV ejection fraction. They found that patients with reduced stroke volume (<35 ml/m^2) were more commonly women and had a lower transvalvular gradient, lower LV diastolic volume index, lower LV ejection fraction, and higher global afterload than patients with normal LV stroke volume (>35 ml/m^2). Importantly, they found that patients with this hemodynamic profile also had a lower 3-year survival compared with patients with normal LV stroke volume (34). Therefore, echocardiographic evaluation of AS severity in elderly women should necessarily include assessment of LV stroke volume index and consideration of the potential impact of small LVOT diameter on discordance between AVA, transvalvular gradient, and dimensionless index in the setting of a normal stroke volume.

Apart from the challenges of echocardiographic diagnosis of severe AS in elderly women, the hemodynamic profile of women identified to have severe AS and referred for TAVR or surgery is different from that in men (10,35). Among patients presenting for TAVR, women typically have more severe stenosis, with a higher mean transaortic pressure gradient and smaller AVA. The smaller AVA in women, however, is largely corrected after indexing values to body surface area (13,36), and the relatively increased transvalvular gradient may be related to better LV systolic function in women undergoing TAVR compared with men as has been previously shown (10,11,16,17,19–21).

Sex differences in the prevalence of low-gradient severe AS among patients presenting for TAVR have also been reported. In one registry, low ejection fraction, low-gradient and PLFLG severe AS were present in 11.7% and 20.8%, respectively (37). Among those with PLFLG severe AS, approximately 60% were female; conversely, the majority of patients with low ejection fraction, low-gradient severe AS were men. Importantly, this latter group had a poorer prognosis than those with either PLFLG or high-gradient severe AS. The poorer mortality of patients with low ejection fraction, low-gradient severe AS, which is predominantly composed of male patients, may partially explain the poorer outcomes observed in men compared with women following TAVR.

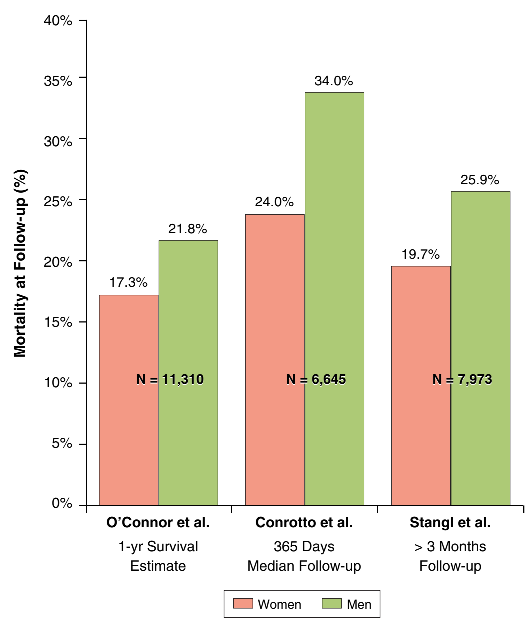
Women presenting with AS also appear to have a higher burden of pulmonary hypertension with a higher mean pulmonary artery pressure and with more women with resting pulmonary artery pressures >60 mm Hg (10,16). Although this may be related to higher transaortic gradients in women, the exact mechanism is unknown and likely multifactorial in this cohort of patients with multiple comorbid conditions that may contribute to pulmonary hypertension.

AVC ON CT IN WOMEN WITH AS

Risk factors for the development of calcific AS have been shown to be similar to those for the development of atherosclerosis (38). However, similar to data showing a lower overall volume of calcification in vascular beds, including the coronary vessels, among women compared with men (39), the degree of aortic valve calcification (AVC) required to produce an equivalent hemodynamic perturbation appears to be less in women compared with men.

The calcium load in the aortic valve has been shown to correlate with AS hemodynamic severity. Accordingly, the utility of quantifying aortic valve AVC by non-invasive imaging has been of interest as a potential clinical tool for confirming the severity of AS in the setting of equivocal echocardiographic findings; as well as in asymptomatic patients for identifying those at increased risk of death and/or needing surgery. Rosenhek et al. (40) evaluated 128 patients with asymptomatic but severe AS using echocardiography and found that the extent of AVC was the only independent predictor of death or AVR. Due to the poor reproducibility and semi-quantitative nature of echocardiographic techniques for quantifying AVC other modalities have been evaluated. CT calcium correlates well with the hemodynamic severity of AS and is also predictive of the progression and adverse outcomes of AS (41,42). It has been previously shown that CT has a role in the diagnosis of severe AS by showing a curvilinear relationship between echocardiographically determined AS severity and the degree of calcium within the aortic valve quantified initially by electron-beam CT (41) and then MDCT (43). They identified an Agatston score cutoff of 1,651 as being 82% sensitive and 80% specific for identifying hemodynamically severe AS. Moreover, they demonstrated that AVC quantification was of diagnostic utility in patients with reduced LV ejection fraction in whom the severity of AS may be underestimated by assessment of transvalvular gradient alone (43). Interestingly, however, it was subsequently shown that the degree of AVC for any given level of AS severity was significantly lower in women compared with men even after correcting for their smaller body size (36). This led to the establishment of separate AVC score cutoffs in men and women for the identification of severe AS (total AVC 2,065 in men and 1,275 in women), which were shown to also be of utility in patients with discordance between AVA and mean transaortic gradient (44). Use of these sex-specific and annulus-size-adjusted measures of AVC ("AVC density") was shown to be predictive of survival in AS patients independent of clinical and echocardiographic factors (45). Apart from having obvious implications for sex-specific cutoffs of AVC for confirming severe AS, these data also highlight potential differences in the pathophysiological interaction between AVC and the development of hemodynamically significant aortic stenosis in women. Importantly, in the study by Clavel et al. (45), the sex variations in AVC cutoffs for predicting outcomes persisted after indexing to body surface area and aortic annulus size, suggesting that additional factors are important in the development of AS gradients in women beyond the degree of "corrected" AVC. Recent data suggest that women may have relatively more valvular fibrosis compared with men. Besides AVC, fibrosis indeed contributes to the development of valvular stenosis and, as opposed to AVC, is not detected by CT (**Figure 2**) (46).

FIGURE 1 **Mortality at Medium-Term Follow-Up Following TAVR in Men and Women**



Mortality stratified by sex based on data from 3 meta-analyses. TAVR = transcatheter aortic valve replacement.

THE MYOCARDIAL RESPONSE TO SEVERE AS IN WOMEN

Apart from anatomic differences in AVC, challenges in the hemodynamic evaluation and severity of AS among women, the myocardial remodeling that occurs in response to pressure overload, and reverse remodeling following correction of severe AS by TAVR or surgery are also different in women versus men. The normal myocardial response to severe AS is characterized by adaptive hypertrophic remodeling in response to increased afterload. Eventually, however, remodeling becomes maladaptive as a result of progressive cell death and fibrosis, and patients decompensate, leading to heart failure (47).

Sex-related differences in the myocardial response to severe AS have been described in terms of both the nature of geometric remodeling and the extent of extracellular fibrosis. Women with severe AS typically manifest more concentric LV geometry, less myocardial fibrosis, and better systolic function compared with men (48,49). This has been observed in large studies of patients presenting for TAVR, with LV ejection fraction consistently shown to be higher in women compared with men (10,11,16,17,19–21). Surgical studies of patients undergoing AVR demonstrate less fibrosis on surgical biopsy of the myocardium in women, and regression of myocardial hypertrophy is also more rapid in women (50). Stangl et al. (20) showed that following TAVR, whereas regression of hypertrophy occurred in men and women,

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improvement of the ejection fraction was significant only in women, potentially reflecting a lower burden of irreversible myocardial damage before TAVR. Recently, Lee et al. (51) showed that although women with moderate-severe AS had less LV hypertrophy and a lower remodeling index, the correlation between these parameters and AS severity was significant in women only, highlighting further sex differences in the pathophysiology of the myocardial response to the hemodynamic load of AS.

Myocardial fibrosis can be identified and quantified pre-TAVR by cardiac magnetic resonance (CMR). Midwall late gadolinium enhancement (LGE) is predictive of outcomes but also of the likely improvement in LV remodeling following AVR (52–54). Azevedo et al. (55) showed that the amount of myocardial fibrosis assessed by histopathology or LGE on CMR is associated with the degree of LV functional improvement and all-cause mortality later after AVR. Sex differences in LGE on CMR remain unclear. Although some authors found no sex differences (51,53,54,56), Dweck et al. (52) observed that there were more women in the LGE negative group. Similarly, Quarto et al. (57). showed that pre-operative LGE predicts risk of major adverse cardiac events and death after AVR, with the LGE-positive groups (“Midwall LGE” and “Infarct LGE”) tending to have proportionately fewer female subjects compared with the LGE-negative group.

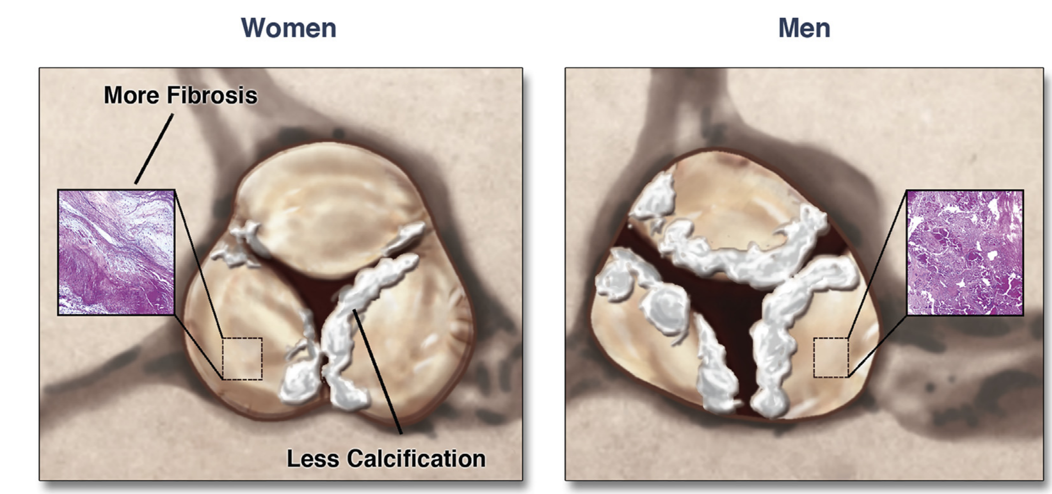
There has also been growing interest in identifying novel imaging markers of myocardial involvement in hemodynamically significant AS. Although the ability of T1 mapping values to accurately discriminate between AS and age-matched controls has been limited in some studies (58), others have shown a significant correlation between native T1 values and severe AS and in distinguishing symptomatic from asymptomatic severe AS, as well as predicting LV mass index and the degree of biopsy-quantified fibrosis (59). There are insufficient sex-specific T1 mapping data in patients with severe AS; however, given the lower burden of fibrosis on surgical biopsy and on LGE imaging in some CMR studies, future investigations are needed to clarify any differences in T1 values in women and men with severe AS to understand the role T1 values may play in risk stratification.

SEX DIFFERENCES IN IMAGING FINDINGS PERFORMED FOR PRE-TAVR EVALUATION

Important differences in the diagnostic imaging findings in women being evaluated before TAVR, particularly with regard to the risk of post-implantation complications are discussed in the following text (Table 2).

ANNULAR DIMENSIONS AND PVR. Among the imaging findings that are pertinent to the pre-TAVR evaluation and that are different in women, the most relevant sex differences are observed for aortic annular size and the implications of this on valve sizing, post-procedural complications, and therefore,

FIGURE 2 **AVC and Fibrosis**

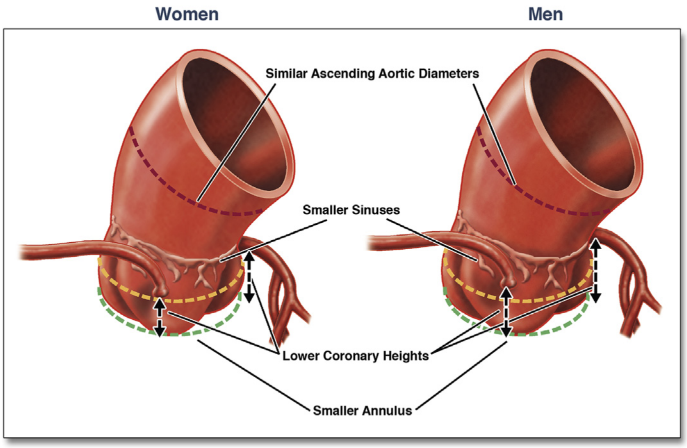


Differences in aortic valve calcification (AVC) and fibrosis are demonstrated in men and women. **Insets** demonstrate the higher burden of fibrosis observed in women compared to men on histopathological evaluation of surgically resected aortic valve tissue.

overall survival. Buellesfeld et al. (60) systematically evaluated TAVR-related MDCT imaging findings among 97 women and 80 men with severe symptomatic AS and found smaller annular and LVOT dimensions in women, but similar ascending aortic dimensions between the sexes (**Figure 3**). The similar ascending aortic dimensions have been attributed to more rapid growth of the ascending aorta in women compared with men in later years of life (61). Women have also consistently been shown to have smaller aortic annuli and LVOT dimensions compared with men in large-registry data. In the patient-level TAVR meta-analysis by O'Connor et al. (10), mean aortic annulus diameter was significantly smaller in women (20.7 ± 3.6 mm vs. 22.8 ± 5.1 mm, respectively; $p < 0.001$).

As expected, smaller aortic annuli in women are associated with the use of smaller THVs compared with men, with larger THVs (26 mm and 29 mm) infrequently used in women compared with men in a 2-centre Canadian registry of predominantly balloon-expandable valves (29.5% vs. 88.8%, $p < 0.001$) (13) and similar findings observed in the German TAVR registry for both self- and balloon-expandable valves (21), as well as in large meta-analyses (10,11). Although the implications of small valve sizes historically related to some elderly women falling out of the range of available devices, this has become less of a problem since the introduction of smaller THV sizes across both self- and balloon-expandable platforms.

FIGURE 3 Aortic Root Size and Coronary Heights



Key anatomic differences in aortic root dimensions are demonstrated between men and women.

TABLE 2 Differences in Imaging Findings Among Women Presenting for TAVR

Aorta and aortic root
Smaller aortic annulus and LVOT diameters resulting in smaller THV sizes
Less aortic valve calcium but more fibrosis
Higher transaortic gradients (at presentation for TAVR)
Higher pulmonary pressures (at presentation for TAVR)
More women in PLFLG severe AS subgroup (similar prognosis to high gradient severe AS post-TAVR)
Fewer women in low-EF, low-gradient severe AS subgroup (poorer survival than PLFLG or high-gradient severe AS post-TAVR)
Lower coronary heights and smaller sinus of Valsalva diameters
Left ventricle
Better LV ejection fraction (at presentation for TAVR)
Less myocardial fibrosis
More pronounced concentric LV remodeling
Peripheral vascular
Less peripheral arterial disease and calcification but smaller iliofemoral luminal diameters

AS = aortic stenosis; EF = ejection fraction; LV = left ventricular; LVOT = left ventricular outflow tract; PLFLG = paradoxical low-flow, low-gradient; TAVR = transcatheter aortic valve replacement; THV = transcatheter heart valve.

Nevertheless, small annular size is still clinically important in terms of TAVR-related complications. Smaller aortic annular dimensions and a likely higher degree of oversizing may be associated with lower rates of paravalvular regurgitation, which is an important determinant of outcomes following TAVR. In a post hoc analysis of the PARTNER trial, Rodes-Cabau et al. (62) showed that patients with a smaller annulus had a significantly lower rate of moderate-severe PVR compared with patients with a large annulus (5.9% vs. 11.5%; $p = 0.009$). Interestingly, the prevalence of significant PVR appears to be reduced in women. Ferrante et al. (18) studied the interaction among PVR, female sex, and survival, and showed that women tended to have lower medium-term mortality than men and lower rates of moderate or greater PVR. Apart from smaller aortic annular size, sex differences in the extent of AVC, a known determinant of PVR (63) as well as the extent of valvular fibrosis may also explain the lower incidence of PVR post-implantation in women.

PROSTHESIS-PATIENT MISMATCH. Prosthesis-patient mismatch (PPM) may also be related to smaller valve sizes in women. Indeed, studies of surgical aortic valve replacement (SAVR) have suggested that women experience PPM at higher rates than men (64), and this has been attributed to smaller valve sizes in female patients. Following TAVR, however, the rates of PPM appear to be lower than that seen with SAVR. Both Pibarot et al. (65) and Popma et al. (66) demonstrated lower rates overall of PPM following

TAVR compared with SAVR, and the difference was more pronounced in the patients with a smaller aortic annulus. Unlike SAVR, annulus size has little effect on the incidence of PPM following TAVR (44,65). A potential explanation for this observation may be that although THVs are stented valves, the stent is thinner, and there is no sewing ring occupying the annular space; therefore, there is less obstruction to blood flow—a difference that is more apparent in a small aortic annulus (65).

Many studies have investigated the impact of sex on post-implantation PPM, and although there was a trend to higher rates of PPM among women in one study (67), most studies have shown that women do not appear to be at increased risk of this complication despite the frequent need for smaller valves (68–70). These data importantly highlight the potential utility of TAVR in women who are surgical candidates but have smaller annular dimensions, given the lower incidence of post-procedural PPM compared with surgery as suggested by some authors (71). Future studies need to directly compare TAVR versus SAVR specifically in this cohort to assess the possible impact of PPM on long-term clinical outcomes.

TAVR FOR FAILED SURGICAL BIOPROSTHESES. There is growing experience with transcatheter valve-in-valve (ViV) as a less invasive treatment strategy for failed surgical valves. ViV treatment is associated with several potential adverse events, including transcatheter device underexpansion, which may be associated with elevated post-procedural gradients and impaired durability (72). Data from the VIVID (Valve-in-Valve International Data) registry showed that mortality after ViV is strongly associated with: 1) physical characteristics of the failing bioprosthetic valve; 2) small surgical valves; and 3) stenosis as the mechanism of failure. Conversely, larger surgical valves and those with predominant regurgitation as the mechanism of failure had relatively better survival (73). Further analyses of the VIVID registry show that cases with predominant stenosis (as opposed to regurgitation) occurred more frequently in women. This was especially the case in large body-size women treated with small surgical valves (label size ≤21 mm). In this subgroup of female patients with what appears to be PPM of the original surgical valve, poorer survival is seen following ViV therapy (D. Dvir, personal communication, January 2016), and other strategies for the treatment of bioprosthetic valve failure may therefore be more suitable (i.e., redo cardiac surgery using a larger valve).

AORTIC ROOT AND ANNULAR RUPTURE RISK. The risk of aortic root and annular rupture appears to be higher in women. In the series reported by Barbanti et al. (74), among the 3,067 patients that underwent TAVR, 37 developed annular rupture. Despite generally equal representation by men and women in the registries included in this study, 74% of the patients who developed annular rupture were women, and annular size was small in their patients overall. After caliper matching patients who experienced rupture with those who did not experience rupture, but who underwent pre-procedural MDCT, further anatomical and procedure-related risk factors were identified, including subannular calcium and oversizing with a balloon-expandable prosthesis >20% by area. The reason for the increased risk in women beyond their smaller annular size remains unclear but raises a number of interesting hypotheses. Perhaps elderly women have more friable tissue that is subject to rupture at a lower threshold than men. Alternatively, the balloon inflation and deployment of the valve may occur more abruptly in women with a smaller annulus, increasing the risk of rupture. Irrespective of mechanism, these data suggest that women with subannular calcium in particular, should be carefully oversized with balloon-expandable devices.

CORONARY OBSTRUCTION RISK. Lower coronary heights and smaller sinus of Valsalva dimensions are also observed in women presenting for TAVR compared with men (60,75). This has important implications for coronary obstruction risk because these dimensions have been shown to be inversely related to the risk of left main obstruction post-implantation, with cutoffs of 12 mm and 30 mm for coronary height and Sinus of Valsalva dimensions, respectively, previously identified as thresholds for increased risk (75,76). Indeed, Ribeiro et al. (75) confirmed that a significantly higher proportion (>80%) of the patients who developed coronary obstruction were women despite relatively equal sex representation in their registries.

PERIPHERAL VASCULAR COMPLICATIONS. Major peripheral vascular complications and major bleeding are also more frequent in women. The primary drivers of vascular complications include reduced femoral diameters relative to the femoral sheath used for the delivery system (sheath-to-femoral artery ratio) and significant vascular calcification. Although women have lower rates of baseline peripheral vascular disease than men Hayashida et al. (77) demonstrated that minimal femoral size is smaller in women compared with men (7.74 ± 1.03 mm vs. 8.55 ± 1.34 mm; $p < 0.001$), and this has been confirmed in larger datasets (10). Despite this, women do not appear to undergo TAVR using nontransfemoral access routes more frequently than men (10), and the differences in femoral diameters may partly explain their higher rate of vascular complications Appropriate use of imaging for pre-TAVR assessment of the iliofemoral vasculature is therefore particularly important in women.

TAVR VERSUS SAVR IN WOMEN

Although women are generally at an increased risk for perioperative morbidity and mortality following SAVR, this is not the case for women undergoing TAVR, where the morbidity and mortality risk is lower compared with men. This intriguing sex-treatment interaction is likely multifactorial and may be related to the fact that women have a smaller chest, smaller aortic root and annular dimensions, and at least among patients presenting for TAVR, a higher rate of porcelain aorta (13). These anatomic characteristics pose important technical challenges and may increase the risk of periprocedural bleeding, myocardial infarction, stroke, and PPM following surgery. Furthermore, women have more pronounced LV concentric remodeling and PLFLG, which are both associated with increased risk of hemodynamic instability, low output syndrome, and mortality following SAVR (78–81). Mohty et al. (79) reported that the combination of PLFLG and PPM, 2 risk factors that are more prevalent in women, is associated with a marked increase in the risk of mortality following SAVR compared with patients without either of these features. The incidence and severity of PPM is also higher in SAVR compared with TAVR. These factors may contribute to the improved outcomes with TAVR compared with SAVR in women.

SUMMARY

Baseline imaging findings are different in women presenting with severe AS and for TAVR evaluation compared with men, including a higher likelihood of AVA-gradient discordance due to smaller LVOT dimensions and more frequent PLFLG severe AS; worse stenosis and a higher burden of pulmonary hypertension at presentation for TAVR; and the development of severe AS at lower valvular calcification thresholds. Women also manifest more concentric remodeling, but less extracellular fibrosis and better baseline LV systolic function. In the pre-TAVR evaluation, diagnostic imaging is important for predicting post-procedure complications that are more frequent in women, including the risk of PPM, annular rupture, coronary obstruction, and major vascular complications. Despite higher rates of immediate post-TAVR complications, mortality rates are lower in women due to a more favorable baseline risk profile and lower rates of significant PVR following TAVR. Moreover, unlike men, women have a more favorable outcome with TAVR compared with SAVR. The potential reduction of PPM risk in patients with small annuli, lower rates of post-procedural PVR and improved survival in women undergoing TAVR may justify treatment with TAVR in intermediate- or even low-risk patients who are still surgical candidates. Randomized studies are needed to address these issues.

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