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REVIEW

Sex Differences in Transcatheter Structural Heart Disease Interventions: How Much Do We Know?

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Abstract

The number of structural heart disease interventions has greatly increased in the past decade. Moreover, interest in the sex-specific outcomes of various cardiovascular conditions and procedures has increased. In this review, we discuss the sex differences in the clinical profiles and outcomes of patients undergoing the most commonly performed structural procedures: transcatheter aortic valve replacement, transcatheter edge to edge repair of the mitral and tricuspid valve, transcatheter pulmonary valve replacement, patent foramen ovale closure and left atrial appendage occlusion. We shed light on potential reasons for these differences and emphasize the importance of increasing the representation of women in randomized clinical trials, to understand these differences and support the application of these cutting-edge technologies.

Keywords: structural heart disease; sex differences; transcatheter interventions; transcatheter aortic valve replacement; transcatheter edge-to-edge repair of the mitral valve; tricuspid interventions; transcatheter pulmonary valve replacement; left atrial appendage occlusion; patent foramen ovale closure

Introduction

With growing evidence from critical randomized controlled trials (RCTs) demonstrating the efficacy of transcatheter interventions in selected patients with various valvular and non-valvular structural heart diseases, the number of these procedures performed in patients with structural heart disease has greatly increased during the past decade [1–5]. Transcatheter aortic valve replacement (TAVR), transcatheter mitral and tricuspid valve edge-to-edge repair (TEER), transcatheter pulmonary valve replacement (TPVR), patent foramen ovale (PFO) closure and left atrial appendage occlusion (LAAO) are among the most frequently performed structural heart procedures. Interest has increased in understanding the differences and clinical factors affecting women receiving these transcatheter therapies, as well as the clinical outcomes of these cutting-edge technologies among women [6]. In this review, we highlight the most recent data on these

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procedures. These sex-based differences in the most commonly performed structural interventions are summarized in Figure 1 and Table 1. We also discuss the importance of increasing the representation of women in RCTs to minimize disparities in care.

Sex-Specific Differences in Patients Undergoing Transcatheter Aortic Valve Replacement

TAVR has become the most commonly performed transcatheter structural heart intervention, as supported by several critical RCTs demonstrating its safety and efficacy in patients with severe aortic stenosis, regardless of their surgical risk [1–6]. The sex-specific outcomes of TAVR have been the subject of several registry studies and meta-analyses [2–5]. An analysis of a large US database, the Transcatheter Valve Therapy (TVT) registry, including 23,652 patients (49.9% women), has indicated that women undergoing TAVR had more comorbidities, were older and had higher Society of Thoracic Surgery (STS) scores than men undergoing TAVR [2]. The investigators have concluded that women had a significantly lower rate of all-cause mortality at 1 year than men (21.3% versus 24.5%, P<0.001), despite their higher rates of short-term complications, including bleeding and vascular complications [2]. These findings are consistent with those based on another global registry, Cerebrovascular EveNts in patients undergoing TranscathetER aortic valve implantation with balloon-expandable valves versus self-expandable valves (CENTER), which included 12,381 patients (58% women). This study has demonstrated that women had more comorbidities, and a higher prevalence of chronic kidney disease and hypertension, than men. At 30 days, no difference between sexes was observed in stroke and all-cause mortality, despite the higher risk of major or life-threatening bleeding in women than men [3]. The Gulf TAVR registry, including 795 patients (44% women), has indicated that women had a lower rate of mortality at 1 year than men (4.3% versus 6.3%)

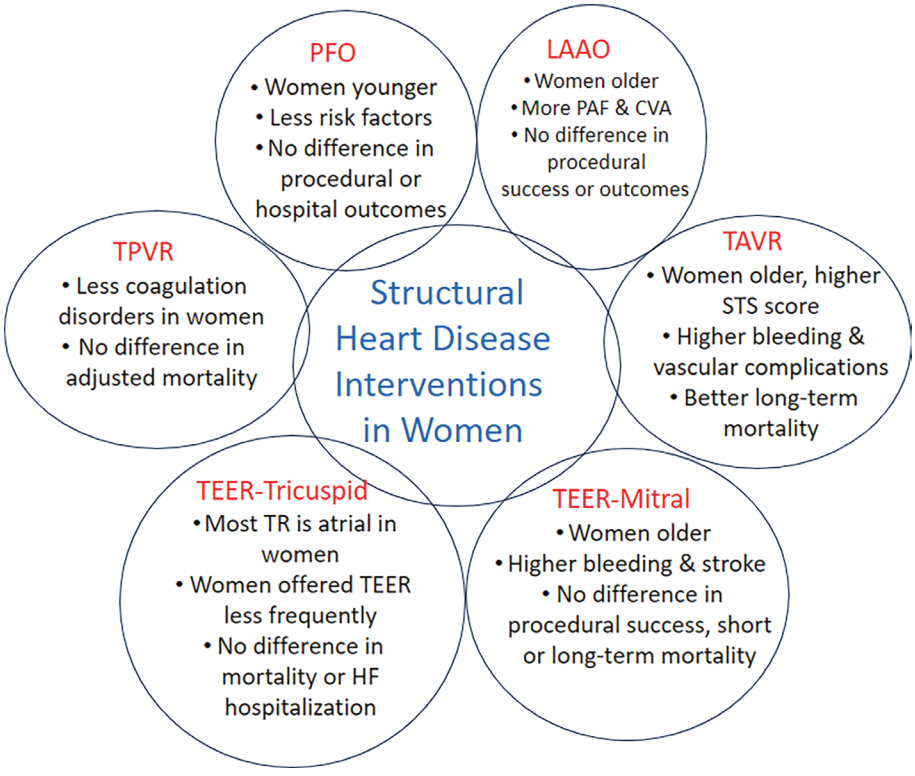

Figure 1 Summary of the Major Sex-Specific Differences in Structural Heart Disease Interventions.
CVA, cerebrovascular events; LAAO, left atrial appendage occlusion; PAF, paroxysmal atrial fibrillation; PFO, patent foramen ovale; STS, Society of Thoracic Surgery; TAVR, transcatheter aortic valve replacement; TPVR, transcatheter pulmonary valve replacement; TEER, transcatheter edge-to-edge repair.

Table 1 Summary of Major Clinical Studies Assessing Sex-Specific Outcomes among Patients Undergoing Transcatheter Structural Heart Interventions.

Procedure	Major studies	Number of patients	Main findings
TAVR	TVT registry [2]	23,652 patients (49.9% women)	• Women were older and had higher STS scores than men. • Women had greater risk of complications, including vascular complications and bleeding, than men. • Women had lower all-cause mortality at 12 months than men.
	CENTER registry [3]	12,381 patients (58% women)	• Women had more comorbidities, including CKD and HTN, than men. • At 30 days, no difference was observed in stroke and all-cause mortality, despite a higher risk of major or life-threatening bleeding in women than men.
	Gulf TAVR [4]	795 patients (44% women)	• Women had lower mortality at 12 months than men.
	Subanalysis of PARTNER II S3 [6]	1661 patients (42% women)	• No significant differences in survival or major strokes based on sex in patients with intermediate or high risk were observed, but higher rates of minor strokes and vascular complications were observed in women than men.
TEER-mitral	Subanalysis of COAPT [17]	614 patients (36% women)	• TEER with the MitraClip, compared with medical therapy alone, improved clinical outcomes, including lower mortality and heart failure hospitalization over 12 months of follow up, regardless of sex.
	Meta-analysis (10 observational studies and 1 subanalysis of the COAPT trial) [18]	24,905 patients (45.6% women)	• Women had higher rates of periprocedural bleeding and stroke than men. • No differences in procedural success, short- and long-term mortality, and heart failure hospitalization at 12 months were observed between men and women.
TEER-tricuspid	Fortmeier et al. [21]	702 patients (55% women)	• The main etiology of functional TR in women is atrial dysfunction, whereas the main etiology of functional TR in men is ventricular dysfunction. • No difference in survival at 24 months was observed.
	TRIVALVE registry [22]	556 patients (56.8% women)	• Women were treated with TEER less frequently than men. • No difference in mortality and heart failure hospitalization at 12 months was observed. • Transcatheter tricuspid interventions, compared with medical therapy alone, were associated with improved survival at 12 months, regardless of sex.
TPVR	Analysis from the National Inpatient Sample [23]	980 hospitalizations (38.5% women)	• The in-hospital mortality was 1.4% for women; no mortality was reported in men (P value = 0.91).
PFO	Retrospective registry from Toronto General Hospital [24]	1032 patients (44.8% women)	• Women were younger, and were less likely to be smokers or have risk factors, such as coronary disease or hyperlipidemia, than men. • No differences in the procedural or in-hospital outcomes, or the recurrence of cerebrovascular events, were observed.

Table 1 (continued)

Procedure	Major studies	Number of patients	Main findings
LAAO	(NCDR) LAA Occlusion Registry, Watchman device [30]	49,357 patients (41.3% women)	• Women were older, and had higher prevalence of paroxysmal atrial fibrillation and previous stroke, than men. • Women had higher periprocedural complications, including pericardial effusion, than men. • No difference in procedural success was observed.
	LAAO prospective study, Amulet device (Abbott) [31]	1088 patients (64.5% women)	• No differences in procedural success, major bleeding, or short- or long-term outcomes at 24 months were observed.

CKD, chronic kidney disease; HTN, hypertension; LAAO, left atrial appendage occlusion; NCDR, National Cardiovascular Data Registry; PFO, patent foramen ovale; STS, Society of Thoracic Surgery; TAVR, transcatheter aortic valve replacement; TPVR, transcatheter pulmonary valve replacement; TEER, transcatheter edge-to-edge repair.

[4]. Another analysis of the sex-specific outcomes of patients with intermediate and high risk in the PARTNER II S3 trial demonstrated that, although women had higher rates of complications, including vascular complications and minor stroke, no significant difference was observed in survival or major strokes according to sex [6]. In summary, the findings from these studies show improved 1-year survival in women after TAVR, despite the greater risk of short-term complications post TAVR in women than men.

The reasons underlying these findings are multifactorial [7–13]. Women undergoing TAVR tend to be older and to have a higher prevalence of comorbidities than men, thus increasing their overall risk of complications [8–10]. Women with severe AS tend to be diagnosed at later ages and often have more severe symptoms than men [11, 12]. Despite prevalent symptoms, aortic valve replacement is performed less often in women than men, and 5-year excess mortality has been observed in women with respect to men [10–13]. Studies have indicated that female sex is associated with a higher risk of vascular complications with TAVR than that associated with male sex, because of women's small vessels, a sheath to femoral artery diameter ratio exceeding 1.05, and high rates of alternative access [8–11]. The lower rates of 1-year mortality in women than men could potentially be explained by the differential response of left ventricular remodeling, in which women demonstrate less advanced remodeling than men in response to a similar severity of aortic stenosis, and have more favorable left ventricular mass regression after TAVR [8, 10, 11]. In contrast, men undergo surgical aortic valve replacement (SAVR) for severe aortic stenosis more frequently than women [11–13]. In addition, studies have shown that SAVR is associated with poorer short-term outcomes in women than men, owing to a higher 30-day mortality after SAVR in women, which is secondary to increased age, higher in-hospital mortality, baseline comorbidities, anatomical differences and frailty [10–13]. No difference in 30-day mortality has been observed between men and women undergoing TAVR. Thus, TAVR has been argued to potentially be even more beneficial and safer among women [13].

Sex-Specific Differences in Patients Undergoing Transcatheter Edge-to-Edge Repair of the Mitral Valve

TEER of the mitral valve can be performed with the MitraClip device or the PASCAL device [14–19]. TEER with the MitraClip (Abbott) has been approved and performed in clinical practice for both primary and secondary mitral regurgitation (MR), on the basis of the results of the Endovascular Valve Edge-to-Edge Repair Study (EVERST II) and Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy (COAPT) trials, respectively [14, 15]. The PASCAL device (Edwards) is a new technology for TEER of the mitral valve, which was approved by the Food and Drug Administration (FDA) in 2022 for primary MR after the results of the CLASP IID trial indicated

that TEER with the PASCAL device is non-inferior to TEER with the MitraClip in patients with primary MR [16]. CLASP IIF (NCT03706833) is an ongoing trial comparing clinical outcomes of patients with secondary MR receiving guideline-directed medical therapy and undergoing TEER with the PASCAL device compared with the MitraClip. Importantly, only the COAPT trial has reported a sex-specific analysis [17].

Several studies have evaluated the sex-specific differences in patients undergoing TEER with the MitraClip device [17, 18]. In a sub-analysis of 614 patients (36% women) of the COAPT TRIAL, the investigators found that TEER with the MitraClip resulted in improvements in clinical outcomes, including lower mortality and heart failure hospitalization, over those with medical therapy alone, during 2 years of follow up, regardless of sex [17]. In a meta-analysis of 11 studies (ten observational studies and one subanalysis of the COAPT trial), although women were found to be at elevated risk of periprocedural complications, including bleeding and stroke, no sex-specific differences were found in procedural success, short- and long-term mortality, and heart failure hospitalization at 1 year [18]. Potential reasons for the higher periprocedural bleeding complications in women than men include women's older age and smaller body size requiring lower doses of periprocedural anticoagulation than the standard dose. In contrast, potential reasons for the elevated risk of periprocedural stroke in women include older age and higher prevalence of atrial arrhythmia and atrial fibrillation than observed in men [17, 18]. Importantly, although these peri-procedural complications are more common in women than men, efforts to formulate strategies to mitigate the risks of such complications in women are essential, because women derive benefits from these interventions despite these complications [18, 19].

Sex-Specific Differences in Patients Undergoing Transcatheter Interventions of the Tricuspid Valve

TEER of the tricuspid valve has evolved as an emerging therapy for patients with symptomatic severe tricuspid regurgitation (TR) despite medical therapy [20–22]. Surgery for patients with severe TR is associated with high mortality and morbidity. TEER of the tricuspid valve offers a less invasive therapeutic option for patients with severe TR, and promising results in the TRILUMINATE trial have recently been reported [20]. The TRILUMINATE study has demonstrated that TEER of the tricuspid valve is safe, decreases TR severity and is associated with improved patient quality of life, on the basis of Kansas City Cardiomyopathy Questionnaire scores [20]. Importantly, no sex-specific analysis was performed for patients undergoing TEER for the tricuspid valve in the TRILUMINATE trial.

One study has assessed the sex-specific outcomes in patients undergoing TEER for TR and has shown that the main etiology of functional TR in women is atrial dysfunction, whereas the main etiology of functional TR in men is ventricular dysfunction [21]. One potential reason for the higher prevalence of atrial TR in women than men is the higher prevalence of atrial arrhythmias in women in general leading to atrial dilation and TR. Although men had higher rates of coronary artery disease than women, no difference was observed in the survival rates between women and men at 2 years (69.9% in women vs 63.7% in men; $P=0.144$) [21]. Similarly, in the TRIVALVE registry, which included 556 patients who underwent transcatheter tricuspid interventions (78.2% TEER, 9.4% annuloplasty, 2.3% transcatheter valve replacement and 10.1% other procedures), women were treated with TEER less frequently than men (74.4% vs. 83.3%, $P<0.01$). Among those undergoing TEER, women received fewer clips than men ($P<0.01$); however, no sex-specific difference in procedural success was observed (79.5% vs. 77.1%, $P=0.56$) [22]. Furthermore, no differences in mortality and heart failure hospitalization at 12 months were observed, and transcatheter tricuspid interventions, compared with medical therapy alone, were associated with improved survival at 12 months, regardless of sex [22].

Sex-Specific Differences in Patients Undergoing Transcatheter Pulmonary Valve Replacement

Limited data are available regarding the sex-specific outcomes of patients undergoing TPVR

[23]. In a retrospective analysis of 980 hospitalizations for TPVR from the National Inpatient Sample, the in-hospital mortality was 1.4% for women, whereas no mortality was reported in men (P value = 0.91) [23]. All patients were discharged within 24 hours, and most patients (95%) were discharged to their homes [23].

Sex-Specific Differences in Patients Undergoing Patent Foramen Ovale Closure

Few studies have assessed sex-specific outcomes in patients undergoing PFO closure [24]. In a retrospective registry from Toronto General Hospital, which included 1032 patients (44.8% women), women were found to be younger, and less likely to be smokers or have risk factors such as coronary artery disease or hyperlipidemia, than men [24]. No difference was observed in the procedural or in-hospital outcomes between women and men undergoing PFO closure [24]. In addition, no sex-specific difference in the rate of recurrence of cerebrovascular events was observed at the short term follow up visit [24].

Another analysis of the Percutaneous Closure of Patent Foramen Ovale in Migraine With Aura (PRIMA) and the Prospective Randomized Investigation to Evaluate Incidence of Headache Reduction in Subjects with Migraine and PFO Occluder Compared with Medical Management (PREMIUM) trials, which included 337 participants randomized to PFO closure or medical therapy, has demonstrated a significant decrease in monthly migraine days, a mean decrease in monthly migraine attacks, and more patients with complete migraine cessation in the PFO closure group ($P \leq 0.05$ for all); these benefits were observed regardless of sex [25].

Sex-Specific Differences in Patients Undergoing Left Atrial Appendage Occlusion

The Watchman device (Boston Scientific) was the first LAAO device approved by the FDA, in 2015, after two major clinical trials, PROTECT AF and PREVAIL, demonstrated that LAAO with the Watchman is non-inferior to warfarin in ischemic stroke reduction in non-valvular atrial fibrillation [26, 27]. Similarly, the Amulet (Abbott) device was FDA approved in 2021 after the Amulet IDE trial, which demonstrated the Amulet device's non-inferiority to the Watchman device [28]. In a patient level analysis of the PREVAIL and PROTECT trials, no differences in freedom from composite efficacy events, including stroke, systemic embolism or cardiovascular/unexplained death were observed according to sex [29].

Few studies have assessed sex-specific outcomes in LAAO [30, 31]. An analysis from the National Cardiovascular Data Registry (NCDR) LAA occlusion Registry including 49,357 patients undergoing LAAO with the Watchman device (41.3% women) has shown that, although the women, compared with the men, were older, had a higher prevalence of paroxysmal atrial fibrillation and previous stroke, and were at greater risk of periprocedural complications, including pericardial effusion, no difference in procedural success according to sex was observed [30]. In another prospective study assessing outcomes after LAAO with the Amulet device (Abbott) in 1088 included patients (64.5% women), no sex-specific differences were observed in procedural success; major bleeding; or short- or long-term outcomes, including ischemic stroke, systemic embolism and cardiovascular death, at 24 months [31]. Importantly, the numeric absolute risk reduction in ischemic stroke was higher in women (from 7.6 to 2.1%/year) than men (from 6.2% to 2.2%/year), thus suggesting a greater benefit of LAAO in women than men [31]. Potential reasons for this finding include older age and higher prevalence of atrial fibrillation in women than men, thus placing women at a greater baseline risk of ischemic stroke than men. Therefore, the numeric reduction of ischemic stroke is probably greater after LAAO in women than men because of their higher baseline risk of stroke.

Representation of Women in Randomized Clinical Trials

Women are relatively under-represented in RCTs, including structural heart disease intervention trials [14, 15, 19, 24–26, 29–34]. Women constituted 42.2% of the patients undergoing TAVR in

the PARTNER 1 trial, 46% of the patients in the PARTNER 2A trial, 32.5% of the patients undergoing TAVR in the PARTNER 3 trial, and 46.9% of the patients undergoing TAVR in the CoreValve Pivotal trial [32–35]. Similarly, women accounted for 33.4% of the patients undergoing TEER with the MitraClip for secondary MR in the COAPT Trial and 38% of the patients who underwent TEER for primary MR in the EVERSTII Trial [14, 15]. In LAAO trials, women composed 32.3% of the patients undergoing LAAO with the Watchman device in the PREVAIL trial, only 29.6% of the patients undergoing LAAO with the Watchman in the PROTECT AF trial [26, 27] and 39.9% of the patients undergoing LAAO with the Amulet device [28]. Even though many cardiac conditions, such as tricuspid regurgitation and atrial fibrillation, are more common in older women than older men, a minority of patients were women in most of these landmark trials. Given that these RCTs form the basis of clinical practice and guidelines, the underrepresentation of women in these trials might have obscured the effectiveness and safety of many novel devices. Women are probably under-represented in these trials for a variety of reasons, including clinical, social and logistical obstacles. Referral bias at both the patient and provider levels, recruitment of patients, evaluation of eligibility at the trial level, and social barriers to enrollment and commitment to follow-up at the patient level are examples of potential influencing factors. These disparities are more prominent among minority groups and became more pronounced during the COVID-19 pandemic [36, 37]. Notably, a recent study has demonstrated that female-led clinical trials achieved more female enrollment and representation in cohorts with atrial fibrillation [38]. This finding highlights the key roles of female leaders and scientist physicians in achieving the goals of enrolling more women in clinical trials, understanding the pathophysiology and etiology underlying sex-specific differences in clinical profile, periprocedural complications and outcomes of structural interventions, and advocating for equity and equality in structural heart care for all patients, regardless of sex.

Conclusions

Sex differences exist in the clinical profiles, periprocedural complications and outcomes among patients undergoing transcatheter therapies for structural heart disease. The reasons for these differences are multifactorial and include differences in age at presentation, the prevalence of comorbidities and anatomical variations between women and men. These differences should motivate us as physicians and leaders to understand the pathophysiology underlying these differences; develop strategies to mitigate the risks and complications whenever feasible and indicated; and commit to enrolling more women in randomized clinical trials, to improve women's representation and diversity, and support the application of various cutting-edge technologies.

Data Availability Statement

All data were extracted from published studies in PubMed and Google Scholar.

Author Contributions

Lina Ya'Qoub performed the literature review, wrote most of the manuscript and edited the manuscript. Jelena Arnautovic and Nadeen Faza reviewed the manuscript and provided constructive feedback and edits. Islam Elgendy provided critical feedback and edits, and supervised the progress of the manuscript.

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Conflict of Interest

The authors have no related conflicts of interest.

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