Supplement to

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Cardiac Interventions TODAY

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It's time to make a difference for **women with aortic stenosis**

Learn about the underdiagnosis, under-referral, and undertreatment of women with aortic stenosis and how we approach this significant healthcare challenge.

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Women With Aortic Stenosis

Assessing the challenges of AS underdiagnosis and under-referral in women.

By Priscilla Wessly, MD, and Renuka Jain, MD

Aortic stenosis (AS) stands as the leading type of valvular heart disease, with a worldwide prevalence of 12.4% in the general population.[1] Notably, the incidence of AS increases with age, indicating a growing risk in an aging population. Established guidelines for the diagnosis and management of AS do not incorporate sex-specific approaches in treatment despite significant research demonstrating sex-based differences in AS presentation, progression, and clinical outcomes.[2-4] Women with AS are underdiagnosed and under-referred, a situation that not only delays critical interventions, such as surgical or transcatheter aortic valve replacement (TAVR), but also results in worse health outcomes for women.[5,6] There are numerous factors that contribute to the underdiagnosis and under-referral of AS in women.

CHALLENGES IN DIAGNOSIS

Women with severe AS have a distinctive patient profile shaped by both physiologic and epidemiologic factors. They tend to present at a later age with atypical symptoms, advanced symptoms, and a higher functional impairment compared with men.[7] Women are more likely to present with New York Heart Association (NYHA) class III-IV heart failure symptoms and renal insufficiency.[8] Despite presenting with more severe symptoms and a higher NYHA class, women frequently underreport the severity of their symptoms.[9] Given these factors, at presentation of the disease, women have higher rates of older age and hypertension, greater renal insufficiency, and a tendency toward frailty.[10] Calculated Society of Thoracic Surgeons (STS) scores are higher in women presenting for treatment, indicating a more challenging surgical risk profile and increased comorbid conditions.[11,12,13]

Sex-based differences are evident in the anatomy, calcification patterns, and fibrosis of patients with AS (Figure 1). Studies have demonstrated that women exhibit distinct patterns of calcification and fibrosis.[10,14] Although there is a strong correlation between the hemodynamic severity of AS and the aortic valve (AV) calcium load as measured by multidetector computed tomography, research has highlighted that women, when compared with men with similar AS severity, present with a lower AV calcium load even after indexing for body surface area and a smaller left ventricular outflow tract.[15] Further studies, such as that by Simard et al, have shown that women are more likely to have greater amounts of valvular fibrosis, localized in dense connective tissue, than men with equivalent hemodynamic AS severity and valve weight density.[16] The extent of fibrosis correlated well with the amount of calcification in men but not in women. Therefore, echocardiographic visualization of calcium on the aortic valve will not correlate with severity of AS in women to the same extent as in men.

Women also typically have smaller aortic annuli relative to their body surface area.[10,14] In a study on AV replacement for severe AS, women constituted 80% of patients with an AV annulus diameter of ≤ 21 mm.[14] Patients with smaller aortic annuli have altered valve hemodynamics, typically characterized by higher gradients and prosthesis-patient mismatch (PPM). This mismatch often results in ineffective regression of left ventricular hypertrophy. In addition, these patients face an increased risk of developing congestive heart failure, diminished exercise capacity and higher mortality rates. Additionally, small prosthesis sizes exacerbate PPM, leading to high gradients that elevate mechanical stress on the valve, potentially accelerating structural valve deterioration.[17-21]

Using echocardiography, women also have been found to have distinct hemodynamic profiles, which makes the diagnosis of severe AS more difficult. Notably, women have a higher incidence of paradoxical low-flow, low-gradient AS with a preserved ejection fraction.[22] This subset of patients, characterized by smaller, hypertrophied left ventricles, presents with unique flow patterns that lead to discordant values of mean gradient and AV area, which can lead to an underdiagnosis of severe AS. Despite having smaller AV areas, larger indexed AV areas, and lower peak velocities and mean gradients than men, women typically have lower stroke volumes, adjusted for body size, compensated by a higher heart rate. The utilization of a unified cutoff for low stroke volume across both sexes in current guidelines fails to capture these sex-specific differences, thereby contributing to the

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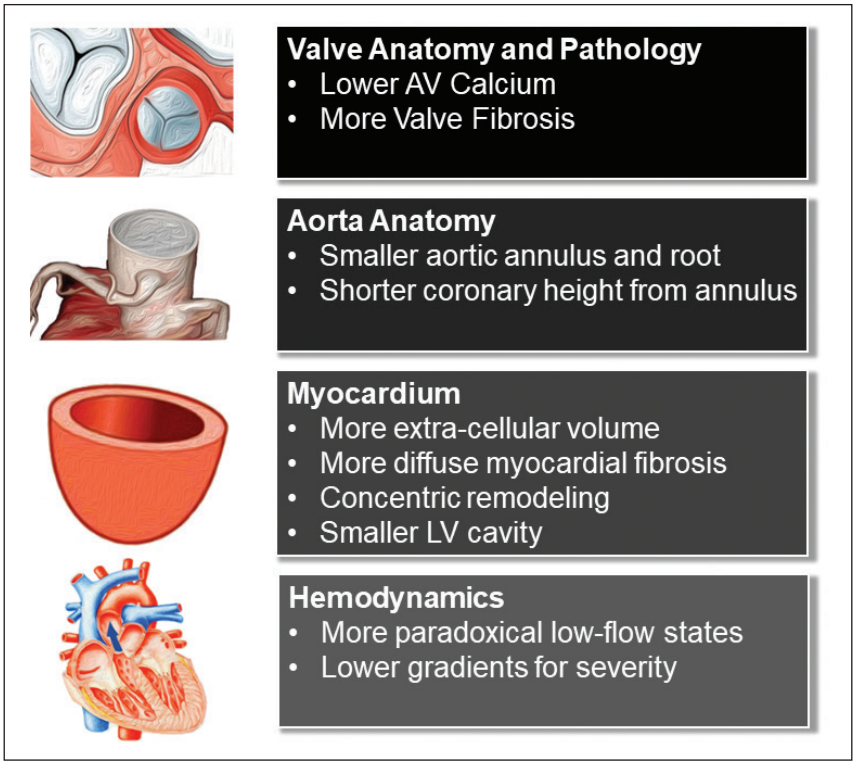

Figure 1. Unique characteristics of AS in women compared with men. LV, left ventricular.

disproportionately high prevalence of low-flow AS with preserved ejection fraction in women.

Sex also influences the pathophysiologic response of the left ventricular myocardium to AS. Studies show that women exhibit smaller left ventricular volume and mass than men but develop more pronounced concentric left ventricular hypertrophy and higher left ventricular ejection fraction. Women more commonly demonstrate normal or concentric remodeling.[23] Notably, women with concentric hypertrophy have a 60% higher risk of all-cause or cardiovascular mortality.[24] Women present with a larger extracellular volume fraction and similar late gadolinium enhancement levels as compared to men. Women developed more diffuse fibrosis than men independent of AS severity.[25] This could serve as an indicator for earlier valve replacement in women; however, further studies are needed.

For these reasons, AS severity is more frequently underestimated in women, leading to delays in diagnosis. There is a critical need for sex-based diagnostic approaches in AS management.[26]

FACTORS THAT CONTRIBUTE TO UNDER-REFERRAL

The underdiagnosis and under-referral of AS in women stem from a complex interplay of clinical, diagnostic, and systemic influences. Women's symptoms are often subtler and less typical, leading to later-stage diagnoses. The absence of sex-specific diagnostic standards further complicates the accurate assessment of AS severity in women, with societal and clinical predispositions favoring more conservative treatment paths. This cautious approach is intensified by the limited inclusion of women in clinical trials, which hampers the development of evidence-based recommendations tailored to their distinct needs. Historical observations from the late 2000s revealed that 69% of patients with severe AS were not referred for AV replacement, with women accounting for 75% of this demographic.[27] The reluctance to refer was mainly owing to presentation with symptoms atypical of AS or the presence of other significant health conditions. By 2017, the percentage of women referred for AV replacement had only marginally improved to 37%.[6]

The advent of TAVR introduced a shift toward improving the sex-based disparity in referrals, yet notable challenges remain. Women now account for 36% to 54% of participants in pivotal TAVR trials, with higher percentages in high- and intermediate-risk groups.[28-35] This persistent disparity gives emphasis to the urgent need for enhanced referral processes and the development of clinical protocols that guarantee equitable treatment for women with AS. Such initiatives are crucial to ensuring that women benefit equally from the latest advancements in valve replacement technologies, ultimately improving outcomes for this underserved population.

Underdiagnosis and referral bias in AS have dire consequences, affecting patient survival and quality of life by causing delays in AV replacement, including TAVR. Delays not only increase mortality but also lead to more frequent emergency department visits and hospitalizations, thereby inflating health care costs and significantly diminishing patient quality of life.[36,37] The risk of sudden cardiac death in patients with asymptomatic severe AS is approximately 1% per year, escalating sharply upon symptom onset, underscoring the need for prompt detection and management.[38,39] The economic implications are profound, with untreated severe AS leading to costly interventions and an increased demand on health care resources. Sex-based disparities also affect treatment outcomes, with women facing higher in-hospital mortality rates, more complications,

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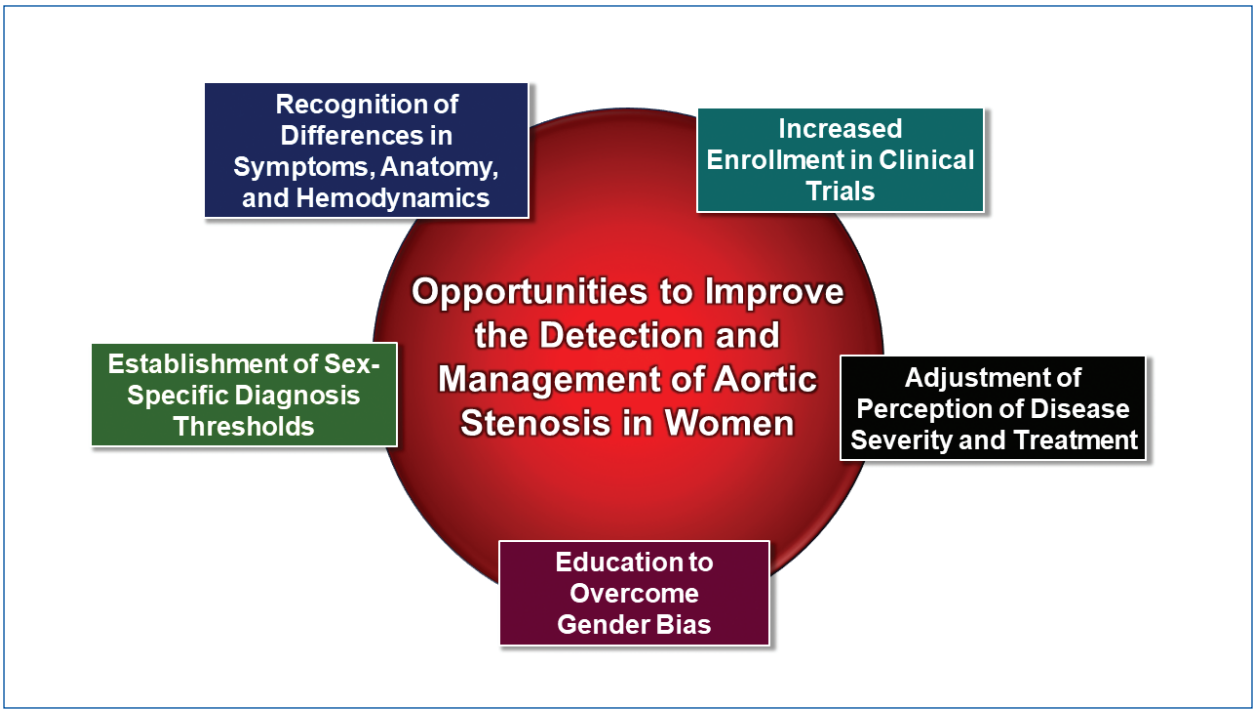

Figure 2. Opportunities to improve diagnosis and referral patterns in women with AS.

and a more challenging recovery, highlighting the critical need for early diagnosis and referral to reduce adverse outcomes in AS, especially among high-risk groups.[6,38]

CLINICAL OUTCOMES WITH AORTIC VALVE REPLACEMENT

There is a differential impact of sex on outcomes between TAVR and surgical AV replacement. Women receiving surgical AV replacement exhibit higher in-hospital mortality rates than their male counterparts. Even after adjusting for risk factors, women tend to experience more vascular complications and require more blood transfusions. Additionally, women are more likely to be discharged to a nursing home or skilled nursing facility after AV replacement.[7] In contrast, with TAVR, outcomes such as 30-day device success, early safety outcomes, permanent pacemaker implantation rates, paravalvular leak, bleeding, and 1-year outcomes did not significantly differ between sexes. However, meta-analyses reveal that women, who make up 48.6% of TAVR recipients, experience higher rates of vascular complications, bleeding events, and strokes. Despite these challenges, they show lower instances of significant moderate to severe paravalvular aortic regurgitation. These findings underscore the need for further research and extended follow-up to fully understand these trends. Remarkably, women displayed a survival advantage over men in TAVR when adjustments were made for baseline demographics, clinical factors, and valve type. Despite the higher rates of complications, there was no difference in mortality between sexes.[40]

The variances in outcomes observed between the sexes after valve replacement can be partially attributed to the differences in left ventricular reverse remodeling. Women tend to show more concentric remodeling and hypertrophy, accompanied by less myocardial fibrosis and superior systolic function compared to men. After TAVR, women exhibit more rapid and pronounced regression in left ventricular mass and dimensions.[41] Additionally, they experience more significant reductions in left ventricular mass index. In conclusion, although women fare worse than men in surgical AV replacement, they fare equally well with TAVR.

CONCLUSION

Despite a similar prevalence of AS in men and women, women face distinct challenges, including atypical clinical presentations, diagnostic complexities, under-referral, and a higher risk of adverse outcomes. These challenges are compounded by systemic biases and a lack of representation in clinical research, leading to a one-size-fits-all treatment approach that fails to account for the unique physiologic and epidemiologic characteristics of women with AS. Addressing these issues through specific strategies such as recognition of symptom and anatomic differences, establishing sex-specific diagnostic thresholds, educating to overcome gender bias, adjusting disease severity perception, and increasing female enrollment in clinical trials is crucial for the tailored, effective management of aortic stenosis in women (Figure 2).

Closing the sex-based gap in AS care is not just a matter of clinical urgency; it is a critical step toward achieving equity in health care outcomes and enhancing the quality of life for all patients with this debilitating condition. ■

1. Osnabrugge RL, Mylotte D, Head SJ, et al. Aortic stenosis in the elderly: disease prevalence and number of candidates for transcatheter aortic valve replacement: a meta-analysis and modeling study. J Am Coll Cardiol. 2013;62:1002-1012. doi: 10.1016/j.jacc.2013.05.015
2. Ito S, Miranda WR, Nkomo VT, et al. Sex differences in LV remodeling and hemodynamics in aortic stenosis: sex-specific criteria for severe stenosis? JACC Cardiovasc Imaging. 2022;15:1175-1189. doi: 10.1016/j.jcmg.2022.02.007
3. Kuneman JH, Singh GK, Milhorini Pio S, et al. Sex differences in left ventricular remodelling in patients with severe aortic valve stenosis. Eur Heart J Cardiovasc Imaging. 2022;23:781-789. doi: 10.1093/ehjci/jeab174
4. Hervault M, Clavel MA. Sex-related differences in calcific aortic valve stenosis: pathophysiology, epidemiology, etiology, diagnosis, presentation, and outcomes. Struct Heart. 2018;2:102-113.
5. Elbaz-Greener G, Rahamim E, Abu Ghosh Z, et al. Sex difference and outcome trends following surgical aortic valve replacement from the National Inpatient Sample (NIS) Database. J Cardiovasc Surg (Torino). Published February 9, 2024. doi: 10.23736/S0021-9509.23.12729-7
6. Chaker Z, Badhwar V, Alqahtani F, et al. Sex differences in the utilization and outcomes of surgical aortic valve replacement for severe aortic stenosis. J Am Heart Assoc. 2017;6:e006370. doi: 10.1161/JAHA.117.006370
7. Fuchs C, Mascherbauer J, Rosenhek R, et al. Gender differences in clinical presentation and surgical outcome of aortic stenosis. Heart. 2010;96:539-545. doi: 10.1136/hrt.2009.186650
8. Tribouilloy C, Bohbot Y, Rusinaru D, et al. Excess mortality and undertreatment of women with severe aortic stenosis. J Am Heart Assoc. 2021;10:e018816. doi: 10.1161/JAHA.120.018816
9. Nau DP, Ellis JJ, Kline-Rogers EM, et al. Gender and perceived severity of cardiac disease: evidence that women are "tougher." Am J Med. 2005;118:1256-1261. doi: 10.1016/j.amjmed.2005.08.006
10. Iribarren AC, AlBadri A, Wei J, et al. Sex differences in aortic stenosis: identification of knowledge gaps for sex-specific personalized medicine. Am Heart J Plus. 2022;21:100197. doi: 10.1016/j.ahjo.2022.100197
11. Szerlip M, Gualano S, Holper E, et al. Sex-specific outcomes of transcatheter aortic valve replacement with the SAPIEN 3 valve: insights from the PARTNER II S3 high-risk and intermediate-risk cohorts. JACC Cardiovasc Interv. 2018;11:13-20. doi: 10.1016/j.jcin.2017.09.035
12. Chandrasekhar J, Dangas G, Yu J, et al. Sex-based differences in outcomes with transcatheter aortic valve therapy: TVT registry from 2011 to 2014. J Am Coll Cardiol. 2016;68:2733-2744. doi: 10.1016/j.jacc.2016.10.041
13. Williams M, Kodali SK, Hahn RT, et al. Sex-related differences in outcomes after transcatheter or surgical aortic valve replacement in patients with severe aortic stenosis: Insights from the PARTNER Trial (Placement of Aortic Transcatheter Valve). J Am Coll Cardiol. 2014;63(15):1522-1528. doi:10.1016/j.jacc.2014.01.036
14. Jander N, Gohlke-Bärwolf C, Bahlmann E, et al. Indexing aortic valve area by body surface area increases the prevalence of severe aortic stenosis. Heart. 2014;100:28-33. doi: 10.1136/heartjnl-2013-304443
15. Aggarwal SR, Clavel MA, Messika-Zeitoun D, et al. Sex differences in aortic valve calcification measured by multidetector computed tomography in aortic stenosis. Circ Cardiovasc Imaging. 2013;6:40-47. doi: 10.1161/CIRCIMAGING.112.980052
16. Simard L, Côté N, Dagenais F, et al. Sex-related discordance between aortic valve calcification and hemodynamic severity of aortic stenosis: is valvular fibrosis the explanation? Circ Res. 2017;120:681-691. doi: 10.1161/CIRCRESAHA.116.309306
17. Leone PP, Regazzoli D, Pagnesi M, et al. Predictors and clinical impact of prosthesis-patient mismatch after self-expandable TAVR in small annuli. JACC Cardiovasc Interv. 2021;14:1218-1228. doi: 10.1016/j.jcin.2021.03.060
18. Tasca G, Brunelli F, Cirillo M, et al. Impact of valve prosthesis-patient mismatch on left ventricular mass regression following aortic valve replacement. Ann Thorac Surg. 2005;79:505-510. doi: 10.1016/j.athoracsur.2004.04.042
19. Herrmann HC, Daneshvar SA, Fonarow GC, et al. Prosthesis-patient mismatch in patients undergoing transcatheter aortic valve replacement: from the STS/ACC TVT registry. J Am Coll Cardiol. 2018;72:2701-2711. doi: 10.1016/j.jacc.2018.09.001
20. Bleiziffer S, Eichinger WB, Hettich I, et al. Impact of patient-prosthesis mismatch on exercise capacity in patients after bioprosthetic aortic valve replacement. Heart. 2008;94:637-641. doi: 10.1136/hrt.2007.116673
21. Rodriguez-Gabella T, Voisine P, Puri R, et al. Aortic bioprosthetic valve durability: incidence, mechanisms, predictors, and management of surgical and transcatheter valve degeneration. J Am Coll Cardiol. 2017;70:1013-1028. doi: 10.1016/j.jacc.2017.07.715
22. Hachicha Z, Dumesnil JG, Bogaty P, et al. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. Circulation. 2007;115:2856-2864. doi: 10.1161/CIRCULATIONAHA.106.668681
23. Kostkiewicz M, Tracz W, Olszowska M, et al. Left ventricular geometry and function in patients with aortic stenosis: gender differences. Int J Cardiol. 1999;71:57-61. doi: 10.1016/s0167-5273(99)00114-x
24. Capoulade R, Clavel MA, Le Ven F, et al. Impact of left ventricular remodelling patterns on outcomes in patients with aortic stenosis. Eur Heart J Cardiovasc Imaging. 2017;18:1378-1387. doi: 10.1093/ehjci/jew288
25. Tastet L, Kwiecinski J, Pibarot P, et al. Sex-related differences in the extent of myocardial fibrosis in patients with aortic valve stenosis. JACC Cardiovasc Imaging. 2020;13:699-711. doi: 10.1016/j.jcmg.2019.06.014
26. Guzzetti E, Poulin A, Annabi MS, et al. Transvalvular flow, sex, and survival after valve replacement surgery in patients with severe aortic stenosis. J Am Coll Cardiol. 2020;75:1897-1909. doi: 10.1016/j.jacc.2020.02.065
27. Freed BH, Sugeng L, Furlong K, et al. Reasons for nonadherence to guidelines for aortic valve replacement in patients with severe aortic stenosis and potential solutions. Am J Cardiol. 2010;105:1339-1342. doi: 10.1016/j.amjcard.2009.12.056
28. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363:1597-1607. doi: 10.1056/NEJMoa1008232
29. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364:2187-2198. doi: 10.1056/NEJMoa1103510
30. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med. 2014;370:1790-1798. doi: 10.1056/NEJMoa1400590
31. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2016;374:1609-1620. doi: 10.1056/NEJMoa1514616
32. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2017;376:1321-1331. doi: 10.1056/NEJMoa1700456
33. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019;380:1695-1705. doi: 10.1056/NEJMoa1814052
34. Thyregod HG, Steinbrüchel DA, Ihlemann N, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic valve stenosis: 1-year results from the All-Comers NOTION Randomized Clinical Trial. J Am Coll Cardiol. 2015;65:2184-2194. doi: 10.1016/j.jacc.2015.03.014
35. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med. 2019;380:1706-1715. doi: 10.1016/j.jacc.2015.03.014
36. Albassam O, Henning KA, Qiu F, et al. Increasing wait-time mortality for severe aortic stenosis: a population-level study of the transition in practice from surgical aortic valve replacement to transcatheter aortic valve replacement. Circ Cardiovasc Interv. 2020;13:e009297. doi: 10.1161/CIRCINTERVENTIONS.120.009297
37. Galper BZ. The TAVR DELAY Registry: rates of early referral to a structural heart team in a large integrated healthcare system. Cath Lab Digest. 2023. Available at https://www.hmpgloballearningnetwork.com/site/cathlab/meeting-update/tavr-delay-registry-rates-early-referral-structural-heart-team-large. Accessed February 29, 2024.
38. Everett RJ, Clavel MA, Pibarot P, et al. Timing of intervention in aortic stenosis: a review of current and future strategies. Heart. 2018;104:2067-2076. doi: 10.1136/heartjnl-2017-312304
39. Perera S, Wijesinghe N, Ly E, et al. Outcomes of patients with untreated severe aortic stenosis in real-world practice. N Z Med J. 2011;124:40-48.
40. O'Connor SA. Revisiting sex equality with TAVR: a colloborative, patient-level meta-analysis of 11,310 patients. J Am Coll Cardiol. 2015;66:221-228. doi: 10.1016/j.jacc.2015.05.024
41. Chen S. Women had favorable reverse left ventricle remodeling after TAVR. Eur J Clin Invest. 2020;50:e13183. doi: 10.1111/eci.13183

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Surgical Perspective on Undertreatment of Aortic Stenosis in Women

Addressing unique challenges, optimizing treatment methods, and the importance of valve performance and hemodynamics for women with AS.

By Sabine Bleiziffer, MD

Calcific aortic stenosis (AS) is one of the most prevalent valve lesions globally and significantly impairs quality of life and survival.[1] Without treatment, 5-year mortality is as high as 94% in patients deemed unsuitable for transcatheter or surgical intervention.[2] Despite advancements in diagnosis and treatment, disparities in the management of AS among different patient demographics, particularly between genders, persist. Women with AS are frequently subjected to undertreatment and substandard care compared to men.[3,4] This article delves into the surgical perspective on the undertreatment of AS in women, highlighting unique challenges, avenues for addressing these issues, optimizing treatment methods, and the importance of valve performance and hemodynamics in this patient population.

UNIQUE ISSUES IN WOMEN WITH AS

The pathophysiology of AS in women presents distinct differences compared to men that may contribute to disparities in diagnosis, treatment, and outcomes. AS in women often presents with more fibrosis and less calcium, while the ventricles have a higher wall thickness, a smaller left ventricular cavity, and a lower left ventricular mass index.[5] Women with AS present with more pronounced symptoms, at an older age and later disease stadium, and with a higher surgical risk.[6] A significant proportion of women present with smaller anatomic structures, including the aortic valve annulus, aortic root, the thoracic cavity, and peripheral vessels, all of which have certain implications on procedure planning and outcomes. Data from a randomized trial showed that 60% of female patients received a surgical valve ≤ 21 mm in label size (vs 13.3% in male patients).[7] From a surgical point of view, the smaller thorax may prevent surgeons from performing minimally invasive procedures in an already small site.[8] The surgeon's gender can also affect surgical outcomes, as shown in a recent analysis in which female patients had better outcomes when operated on by a female surgeon.[9]

ADDRESSING UNDERTREATMENT

There is a tendency for a gender bias in the clinical setting, where the symptoms reported by women may be misinterpreted by both female patients and physicians, attributing symptoms to noncardiac causes. This lack of awareness is thought to be the most common reason why diagnosis and treatment of AS is delayed in women.[10] In a cohort of 2,429 consecutive patients with diagnosed severe AS (49.5% women), women were less likely to undergo aortic valve replacement.[11] The IMPULSE study demonstrated that female patients more often received a transcatheter treatment than surgical valve replacement, which seems reasonable given the older age and higher surgical risk at the time of presentation.[6] Addressing the undertreatment of AS in women requires a multifaceted approach. First, it is crucial to enhance awareness among health care providers about the gender-specific manifestations and risks associated with AS. Interdisciplinary heart teams—including cardiologists, cardiovascular surgeons, and imaging specialists—should adopt a gender-inclusive approach to decision-making. Patient education also plays a vital role; women should be informed about the significance of their symptoms and the potential risks of delaying treatment, empowering them to advocate for timely and appropriate care.

OPTIMIZING TREATMENT METHODS

The recent findings indicating elevated mortality rates after surgical aortic valve replacement (SAVR) in women are cause for concern and warrant focused attention.[8,11,12] It is required to integrate gender-specific considerations into the decision-making process for selecting the most appropriate intervention (transcatheter aortic valve replacement [TAVR] vs SAVR) and ensure meticulous procedural

planning to tailor the approach to individual patient needs. TAVR, being less invasive, may be particularly beneficial for women who are at higher risk of complications from open surgery. Moreover, women are at an increased risk of receiving smaller prosthetic valves, leading to a higher incidence of patient-prosthesis mismatch (PPM), a factor that can adversely affect various outcomes.[13] Effective procedural planning should incorporate strategies for predicting the optimal prosthesis type and size, determining the most suitable access route, and assessing the need for aortic root enlargement. From a surgical perspective, it is imperative to promote education among surgeons regarding the benefits of minimally invasive techniques for women. Contrary to some opinions suggesting increased procedural challenges in women, some authors indicate that with proper training and technique adaptation, these challenges can be effectively managed.[14]

Data of the SMART trial were recently published,[15] and results of the RHEIA trial are expected with the year.[16] These recent randomized trials, which focus on small anatomies and women with AS, will potentially influence future guidelines and practice standards.

SIGNIFICANCE OF VALVE PERFORMANCE AND HEMODYNAMICS

The performance of a prosthetic valve and its hemodynamic characteristics, aiming for low gradients and the absence of regurgitation, are crucial for relieving symptoms, improving exercise tolerance and quality of life, and enhancing survival. In addition, good hemodynamics are associated with durability and the long-term benefit of a valve replacement procedure.[17] In the smaller-sized aortic root anatomy of women, the concept of supra-annular valves may optimize valve opening area and gradients during SAVR and TAVR and minimize the risk of PPM.[18,19] The guidelines even recommend a transcatheter rather than a surgical procedure if the risk for PPM is high.[20] For patients undergoing SAVR, aortic root or annulus enlargement has been shown to allow implantation of a larger valve, but the risks and benefits have to be balanced.[21] To achieve the best possible hemodynamics, a meticulous preprocedure planning of valve type and size and potential concomitant procedures such as annular enlargement is key.

CONCLUSION

The underdiagnosis and undertreatment of AS in women is a multifactorial issue. By recognizing and addressing the unique challenges faced by women with AS, diagnostic and treatment strategies can be adopted accordingly. Emphasizing the importance of valve performance and hemodynamic optimization can significantly improve the outcomes for women with AS. It is imperative that gender-specific research and clinical trials are executed to fill the existing knowledge gaps. ■

1. Coffey S, Roberts-Thomson R, Brown A, et al. Global epidemiology of valvular heart disease. Nat Rev Cardiol. 2021;18:853-864. doi: 10.1038/s41569-021-00570-z
2. Kapadia SR, Leon MB, Makkar RR, et al. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet. 2015;385:2485-2491. doi: 10.1016/S0140-6736(15)60290-2
3. Elbaz-Greener G, Rahamim E, Abu Ghosh Z, et al. Sex difference and outcome trends following surgical aortic valve replacement from the National Inpatient Sample (NIS) Database. J Cardiovasc Surg (Torino). Published February 9, 2024. doi: 10.23736/S0021-9509.23.12729-7
4. Gaede L, Sitges M, Neil J, et al. European heart health survey 2019 [published correction appears in Clin Cardiol. 2021 May;44:731]. Clin Cardiol. 2020;43:1539-1546. doi: 10.1002/clc.23478
5. Dobson LE, Musa TA, Uddin A, et al. Gender influences left ventricular remodelling in the setting of aortic stenosis but does not appear to impact on reverse remodelling following transcatheter aortic valve implantation. J Cardiovasc Magn Reson. 2015;17(Suppl 1):P332. doi: 10.1186/1532-429X-17-S1-P332
6. Steeds RP, Messika-Zeitoun D, Thambyrajah J, et al. IMPULSE: the impact of gender on the presentation and management of aortic stenosis across Europe. Open Heart. 2021;8:e001443. doi: 10.1136/openhrt-2020-001443
7. Van Mieghem NM, Reardon MJ, Yakubov SJ, et al. Clinical outcomes of TAVI or SAVR in men and women with aortic stenosis at intermediate operative risk: a post hoc analysis of the randomised SURTAVI trial. EuroIntervention. 2020;16:833-841. doi: 10.4244/EIJ-D-20-00303
8. Elhmidi Y, Piazza N, Mazzitelli D, et al. Sex-related differences in 2197 patients undergoing isolated surgical aortic valve replacement. J Card Surg. 2014;29:772-778. doi: 10.1111/jocs.12442
9. Wallis CJD, Jerath A, Coburn N, et al. Association of surgeon-patient sex concordance with postoperative outcomes. JAMA Surg. 2022;157:146-156. doi:10.1001/jamasurg.2021.6339
10. Nau DP, Ellis JJ, Kline-Rogers EM, et al. Gender and perceived severity of cardiac disease: evidence that women are "tougher." Am J Med. 2005;118:1256-1261. doi: 10.1016/j.amjmed.2005.08.006
11. Tribouilloy C, Bohbot Y, Rusinaru D, et al. Excess mortality and undertreatment of women with severe aortic stenosis. J Am Heart Assoc. 2021;10:e018816. doi: 10.1161/JAHA.120.018816
12. Dagan M, Yeung T, Stehli J, et al. Transcatheter versus surgical aortic valve replacement: an updated systematic review and meta-analysis with a focus on outcomes by sex. Heart Lung Circ. 2021;30:86-99. doi: 10.1016/j.hlc.2020.05.112
13. Dayan V, Vignolo G, Soca G, et al. Predictors and outcomes of prosthesis-patient mismatch after aortic valve replacement. JACC Cardiovasc Imaging. 2016;9:924-933. doi: 10.1016/j.jcmg.2015.10.026
14. Wilbring M, Matschke KE, Alexiou K, et al. Surgery without scars: right lateral access for minimally invasive aortic valve replacement. Thorac Cardiovasc Surg. 2021;69:461-465. doi: 10.1055/s-0040-1713137
15. Herrmann HC, Mehran R, Blackman DJ, et al. Self-expanding or balloon-expandable TAVR in patients with a small aortic annulus. N Engl J Med. Published online April 7, 2024. doi:10.1056/NEJMoa2312573
16. Eltchaninoff H, Bonaros N, Prendergast B, et al. Rationale and design of a prospective, randomized, controlled, multicenter study to evaluate the safety and efficacy of transcatheter heart valve replacement in female patients with severe symptomatic aortic stenosis requiring aortic valve intervention (Randomized researcH in womEn all comers wIth Aortic stenosis [RHEIA] trial). Am Heart J. 2020;228:27-35. doi: 10.1016/j.ahj.2020.06.016
17. Ochi A, Cheng K, Zhao B, et al. Patient risk factors for bioprosthetic aortic valve degeneration: a systematic review and meta-analysis. Heart Lung Circ. 2020;29:668-678. doi: 10.1016/j.hlc.2019.09.013
18. Ruzicka DJ, Hettich I, Hutter A, et al. The complete supraannular concept: in vivo hemodynamics of bovine and porcine aortic bioprostheses. Circulation. 2009;120(11 Suppl):S139-S145. doi: 10.1161/CIRCULATIONAHA.109.844332
19. Abdelghani M, Mankerious N, Allali A, et al. Bioprosthetic valve performance after transcatheter aortic valve replacement with self-expanding versus balloon-expandable valves in large versus small aortic valve annuli: insights from the CHOICE trial and the CHOICE-Extend registry. JACC Cardiovasc Interv. 2018;11:2507-2518. doi: 10.1016/j.jcin.2018.07.050
20. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease [published correction appears in Eur Heart J. 2022 Feb 18]. Eur Heart J. 2022;43:561-632. doi: 10.1093/eurheartj/ehab395
21. Sá MPBO, Zhigalov K, Cavalcanti LRP, et al. Impact of aortic annulus enlargement on the outcomes of aortic valve replacement: a meta-analysis. Semin Thorac Cardiovasc Surg. 2021;33:316-325. doi: 10.1053/j.semtcvs.2020.06.046

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The Crucial Role of the Heart Team

Aortic stenosis in women: a heart team approach.

By Puja B. Parikh, MD, MPH, FACC, FAHA, FSCAI

During the past decade, the multidisciplinary heart team (MDHT) has significantly evolved with respect to its composition, function, and management paradigms. MDHTs have progressed to comprise primary cardiologists, interventional cardiologists, cardiac surgeons, cardiac imaging specialists, cardiac anesthesiologists, advanced practice clinicians (ie, structural heart/valve program coordinator), advanced heart failure cardiologists, cardiac electrophysiologists, vascular surgeons, neurologists, and multiple internal medicine specialists, including oncologists, nephrologists, and infectious disease specialists (Figure 1). The American and European professional societies have given a class I recommendation for MDHT assessment in all patients with severe valvular heart disease for whom valvular intervention is being considered.[1,2] Because the treatment options for valvular heart disease have widely expanded with the development of novel transcatheter devices and approaches, the value of an MDHT has become increasingly apparent to ultimately promote improved medical decision-making and optimize management of complex patients and their respective clinical outcomes.[3] The preference of the most important stakeholder in this shared decision-making process has always been that of the patient.

Prior to its formal implementation in randomized controlled trials[4] and eventual guideline adaptation,[1,2] the MDHT approach has remained a central mainstay in the management of patients with severe aortic stenosis (AS). Before the commercialization of transcatheter aortic valve replacement (TAVR), it was quite common for the cardiac surgeon to serve as the "gatekeeper" for valvular intervention and for referring primary cardiologists and cardiac surgeons to discuss a patient's risk profile and the utility (or futility) of surgical aortic valve replacement (SAVR) and possible concomitant surgical procedures (coronary artery bypass graft (CABG) surgery, mitral/tricuspid valve surgery, ascending aortic aneurysm repair, root enlargement, etc.) in patients with severe AS.

Times have changed and the introduction of disruptive transcatheter technologies has produced multiple options for valvular intervention and numerous questions for the MDHT to address, including choice of initial valvular intervention strategy (ie, SAVR vs TAVR), choice of surgical and/or transcatheter heart valve (THV) type, choice of approach in patients with peripheral arterial disease (PAD) (ie, transfemoral with peri-TAVR peripheral intervention versus alternative access), type of alternative access, choice to intervene on pre-existing carotid stenosis, and the choice of whether to perform percutaneous coronary intervention (PCI) on severe coronary artery disease (CAD) and in which vessels to perform PCI in the setting of multivessel CAD. Patient populations that have always been the most controversial in MDHT discussions have included younger patients, patients with comorbid high-risk cardiovascular conditions (severe CAD, significant mitral/tricuspid disease, severe PAD, etc.) and/or noncardiac conditions (eg, masses/malignancy, infectious disorders, bleeding diatheses, etc.), patients with failed bioprosthetic valve (surgical or transcatheter), patients with bicuspid aortic valve, and of course, patients (predominantly women) with small aortic annulus.

ROLE OF THE MDHT IN EVALUATING WOMEN WITH SEVERE AS

Women with severe AS are frequently diagnosed at later ages compared to men and often are more symptomatic with higher rates of New York Heart Association class III and IV heart failure compared to men, despite similar severity of AS.[5] They often experience higher mortality than their male counterparts with AS, who are more prone to undergoing aortic valve replacement.[5] Although early outcomes after aortic valve replacement (SAVR or TAVR) are similar in men and women, women undergoing TAVR have improved long-term outcomes over men, whereas those undergoing SAVR have worse long-term outcomes.[5-8]

In numerous MDHT discussions of women with severe AS, it has become well apparent that sex-related disparities

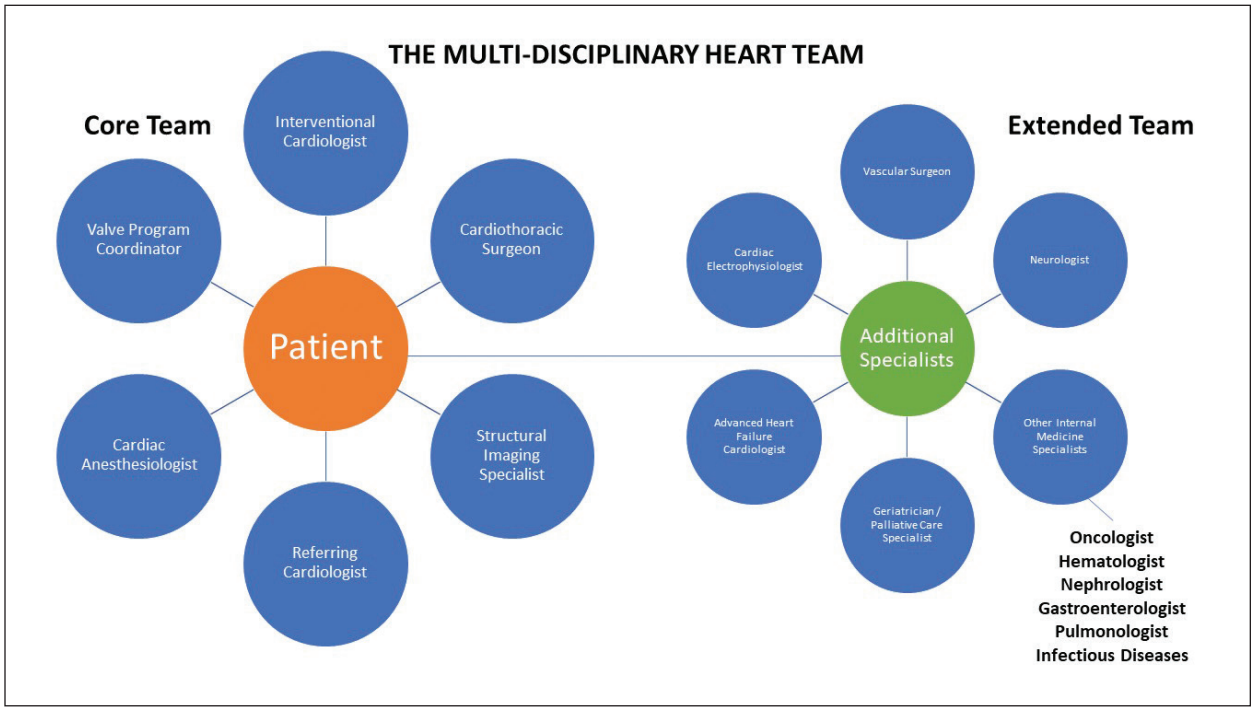

Figure 1. The Multidisciplinary Heart Team.

in adaptation to AS exist. Women often have greater left ventricular (LV) wall thickness and smaller LV cavities, along with narrow outflow tracts and smaller aortic annuli.[9] When undergoing SAVR, women more frequently receive smaller prosthetic valves and concomitant aortic root enlargements, and suffer worse outcomes, including higher bleeding rates (eg, transfusion requirements) compared to men.[8,10] TAVR may be the preferred treatment option in women with small aortic annuli, given the lower incidence of patient prosthesis mismatch, which has been associated with higher morbidity and mortality.[11,12] Selection of transcatheter heart valve type and size also warrants further discussion among the MDHT for optimization of later term outcomes.[13]

The MDHT's responsibilities in weekly team meetings or during consultation in the inpatient/outpatient setting are to assess the patient's severity of AS and symptom profile, determine the appropriateness of valvular intervention, and have a thorough discussion of risks, benefits, and alternatives in these patients. Deciphering a patient's severity of disease often involves interpretation of invasive and noninvasive hemodynamics along with multimodality imaging by the interventional cardiologist, structural imaging specialist, cardiac surgeon, and the referring cardiologist. Since the approval of TAVR for patients at low surgical risk in the United States in 2019, the emphasis on surgical risk assessment through formal calculators like the Predicted Risk of Mortality from the Society of Thoracic Surgery has lessened. Furthermore, TAVR risk calculators have focused on early outcomes rather than late-term outcomes. The decision of the MDHT to proceed with valvular intervention must be coupled with risk/benefit assessment of surgical or transcatheter intervention, taking into account the patient's preferences via shared decision-making. Identification of patients with AS in whom aortic valve intervention is futile remains a challenging task for the MDHT and may sometime require further assessment with palliative care or geriatric specialty consultations. Hence, it is vital for the MDHT to provide their assessments of women with AS across a broad spectrum of patient age, symptom profile, functional status, comorbidities, and anatomic conditions, including bicuspid aortic valve, small aortic annuli, small sinuses, and coronary heights. Management of concomitant CAD in women with AS often requires MDHT discussion when deciding management strategy (eg, CABG versus single/multivessel PCI versus medical therapy). Concomitant mitral and/or tricuspid disease, which have been shown to be associated with worse outcomes in patients undergoing aortic valve replacement,[14,15] also warrants dialogue from the MDHT regarding a decision to intervene and possibly the optimal sequence of interventions. The younger woman presenting with AS or a failed bioprosthetic valve frequently merits MDHT interchange regarding the optimal strategy for lifetime management of AS in this patient population.

FURTHER CONSIDERATIONS FOR THE MDHT

In the United States, significant variability is present in the operations and composition of MDHTs. While evaluation and optimization of patient outcomes have

always been a top priority, their importance has been further emphasized in the current era of public reporting. The primary focus of optimizing death and stroke rates in patients undergoing TAVR has been coupled with further attention to other publicly reported outcomes, including bleeding, acute kidney injury, and significant paravalvular leak. Cost effective strategies are also discussed among the MDHT, with suggestions for reducing procedural costs (eg, selection of intraprocedural equipment, staffing, etc.) and hospital costs (eg, shorter hospital length of stay, fast-tracking postprocedural care on telemetry units instead of intensive care units, classification of higher diagnosis-related group in patients with major comorbid conditions, promoting TAVR to be done as outpatient [as opposed to inpatient], etc.). Weekly MDHT meetings are frequently run by valve program coordinators, who set the agenda, record attendance and minutes, present new patient cases and upcoming schedules, mediate discussions for complex cases, and ensure appropriate specialists beyond the core team are present as needed. Although these MDHT meetings are a requirement for TAVR reimbursement, the prolonged time spent discussing complex AS cases typically is not reimbursed to the participants involved.

Furthermore, the extensive workup required for pre-TAVR patients can be a burden not only for the referring cardiologist but also the patient and their caregiver. Strategies to create seamless care for optimal satisfaction of all stakeholders are warranted. Weekly clinics with multiple members of the MDHT allow for patient convenience with swift decision-making, but may be difficult for the individual providers with respect to scheduling and other clinical and nonclinical (eg, educational or administrative) responsibilities. Effective communication between the MDHT with patients and their referring cardiologists and/or primary medical doctor remains of utmost importance for all stakeholders involved.

SUMMARY

Ultimately, the MDHT has been and continues to be vital for optimal management and outcomes in patients with valvular heart disease, as well as numerous other cardiac conditions. Specifically, the MDHT plays a critical role in all aspects of care in women with AS, from education of the primary medical providers regarding the under-treatment of AS in this population, the interpretation of discordant imaging data, the management of co-morbid conditions, procedural planning (i.e. type of procedure, surgical/transcatheter heart valve type and size, access, etc), and optimization of postprocedural care. As additional technologies and newer data develop, the central role the MDHT plays may be challenged by time constraints of individual specialty members and the absence of reimbursement for prolonged discussions of complex patients. Additional understanding is needed for the types of patient cases that benefit from MDHT evaluations, as well as further optimization of MDHT practices to provide seamless care for patients and referring providers and concomitantly minimizing the challenges for MDHT participants. ■

1. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2021;77:450-500. doi: 10.1016/j.jacc.2020.11.035
2. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J. 2022;43:561-632. doi: 10.1093/eurheartj/ehab395
3. Nishimura RA, O'Gara PT, Bavaria JE, et al. 2019 AATS/ACC/ASE/SCAI/STS expert consensus systems of care document: a proposal to optimize care for patients with valvular heart disease: a joint report of the American Association for Thoracic Surgery, American College of Cardiology, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2019;73:2609-2635. doi: 10.1016/j.jacc.2018.10.007
4. Makkar RR, Fontana GP, Jilaihawi H, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis. N Engl J Med. 2012;366:1696-1704. doi: 10.1056/NEJMoa1202277
5. Tribouilloy C, Bohbot Y, Rusinaru D, et al. Excess mortality and undertreatment of women with severe aortic stenosis. J Am Heart Assoc. 2021;10:e018816. doi: 10.1161/JAHA.120.018816
6. Wang TY, Gracia E, Callahan S, et al. gender disparities in management and outcomes following transcatheter aortic valve implantation with newer generation transcatheter valves. Am J Cardiol. 2019;123:1489-1493. doi: 10.1016/j.amjcard.2019.01.048
7. Novotny S, Kort S, Tannous H, et al. Predictors of 1-year mortality in men versus women undergoing transfemoral transcatheter aortic valve implantation. Am J Cardiol. 2023;186:1-4. doi: 10.1016/j.amjcard.2022.10.018
8. Parikh PB, Wang TY, Sharma N, at al. Sex-related differences in early- and long-term mortality after transcatheter and surgical aortic valve replacement: a systematic review and meta-analysis. J Invasive Cardiol. 2020;32:295-301.
9. Carroll JD, Carroll EP, Feldman T, et al. Sex-associated differences in left ventricular function in aortic stenosis of the elderly. Circulation. 1992;86:1099-1107. doi: 10.1161/01.cir.86.4.1099
10. Morris JJ, Schaff HV, Mullany CJ, et al. Gender differences in left ventricular functional response to aortic valve replacement. Circulation. 1994;90(5 Pt 2):II183-189.
11. Pibarot P, Weissman NJ, Stewart WJ, et al. Incidence and sequelae of prosthesis-patient mismatch in transcatheter versus surgical valve replacement in high-risk patients with severe aortic stenosis: a PARTNER trial cohort — a analysis. J Am Coll Cardiol. 2014;64:1323-1334. doi: 10.1016/j.jacc.2014.06.1195
12. Head SJ, Mokhles MM, Osnabrugge RL, et al. The impact of prosthesis-patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27,186 patients with 133,141 patient-years. Eur Heart J. 2012;33:1518-1529. doi: 10.1093/eurheartj/ehs003
13. Herrmann HC, Mehran R, Blackman DJ, et al. Self-expanding or balloon-expandable TAVR in patients with a small aortic annulus. N Engl J Med. Published online April 7, 2024. doi: 10.1056/NEJMoa2312573
14. Généreux P, Pibarot P, Redfors B, et al. Evolution and prognostic impact of cardiac damage after aortic valve replacement. J Am Coll Cardiol. 2022;80:783-800. doi: 10.1016/j.jacc.2022.05.006
15. Parikh PB, Mack M, Stone GW, et al. Transcatheter aortic valve replacement in heart failure. Eur J Heart Fail. 2024;26:460-470. doi: 10.1002/ejhf.3151

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Understanding the Impact of TAVR in Women With Small Aortic Annulus

Insights into the SMART trial.

By Mauro Gitto, MD; Birgit Vogel, MD; Roxana Mehran, MD; Howard C. Herrmann, MD; and Didier Tchétché, MD

The SMall Annuli Randomized To Evolut or SAPIEN (SMART) trial compared the latest iterations of self-expanding and balloon-expandable transcatheter heart valves (THVs) in patients with a small aortic annulus undergoing transcatheter aortic valve replacement (TAVR). A small aortic annulus is highly prevalent among women undergoing TAVR, who constituted 87% of the randomized patients. This editorial aims to summarize the key findings of the SMART trial and their relevance for women with aortic stenosis (AS).

BACKGROUND, RATIONALE AND DESIGN OF THE SMART TRIAL

AS is a prevalent valve disorder in the aging population of Western countries. Among elderly AS patients, women, who generally have longer life expectancies, constitute a significant proportion.[1] In comparison to men, women undergoing TAVR display distinct clinical features and unique anatomic characteristics, which encompass a higher prevalence of fibrosis over calcification as the primary mechanism of leaflet degeneration, as well as smaller annular and left ventricular outflow tract dimensions, despite similar aortic root anatomy.[2,3] A small aortic annulus, commonly defined as an aortic valve area ≤ 430 mm^2, is notably more prevalent in women compared to men with AS. In the TAVI-SMALL registry, a retrospective study involving 859 patients with small annulus undergoing TAVR with self-expanding valves, 90% of participants were women.[4]

The presence of a small aortic annulus has been linked to increased postprocedural aortic gradients and prosthesis-patient mismatch (PPM) after both TAVR and surgical aortic valve replacement (SAVR).[5,6] Notably, female sex, along with small valve size and balloon-expandable and intra-annular THV designs, have been identified as independent predictors for PPM.[7,8] As TAVR is increasingly performed in younger and less comorbid patients, there is a growing recognition of the need to evaluate PPM as a surrogate endpoint for long-term adverse events.[4,7] A meta-analysis involving 81,969 TAVR patients from 23 studies indicated that severe PPM, defined by an indexed effective orifice area < 0.65 cm^2/m^2, had an incidence of 10.9%, and was associated with increased 5-year mortality (hazard ratio [HR], 1.25; 95% CI, 1.16-1.36).[9] Additionally, increased aortic mean gradients after TAVR are the main determinant of hemodynamic structural valve deterioration (SVD), a surrogate for TAVR durability, impacting mortality and heart failure hospitalizations, as observed in the pooled CoreValve US Pivotal and SURTAVI analyses.[10]

Most available data on TAVR in small aortic annuli are derived from retrospective cohorts or secondary trial analyses, highlighting an unmet need for randomized trials focused on this patient population. The recently published VIVA trial, which randomized 151 patients (93% women) with severe AS and a small annulus to either TAVR or SAVR, showed no differences in terms of severe PPM and moderate-severe aortic regurgitation at 60 days.[11] However, the rate of severe PPM was numerically higher with SAVR as compared to TAVR (10.3% vs. 5.6%) and, with only 52% of the estimated sample size being finally enrolled, the study was underpowered for its primary endpoint.

The SMART Trial (NCT04722250) is an international, prospective, multicenter, randomized controlled, post-market trial designed to assess the noninferiority in terms of clinical outcomes and hemodynamic superiority of the Evolut supra-annular self-expanding THV (Medtronic) as compared to the Sapien intra-annular balloon-expandable system (Edwards Lifesciences) (Figure 1).[12] Patients with

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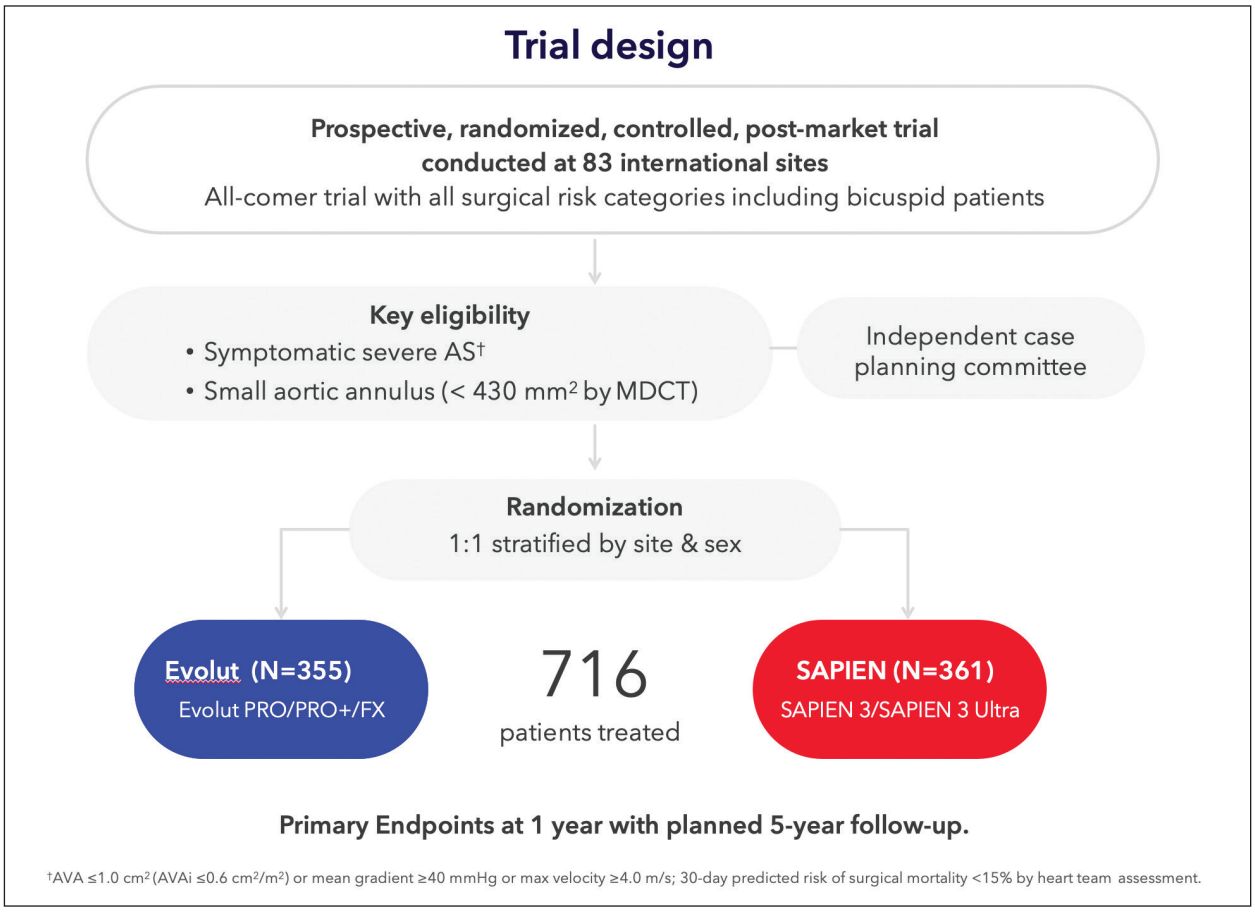

Figure 1. SMART Trial study design.

severe symptomatic AS and a small aortic annulus have been enrolled and randomized to receive TAVR with either the Evolut R/PRO/PRO+/FX self-expanding or the Edwards Sapien 3/3 Ultra balloon expandable valve (Figure 2).

The two powered coprimary endpoints at 12-month follow-up were (1) the composite of mortality, disabling stroke, or rehospitalization for heart failure (powered for noninferiority), and (2) Bioprosthetic valve dysfunction (BVD; powered for superiority). BVD was defined as a composite of: hemodynamic structural valve dysfunction (HSVD), defined as an aortic valve mean gradient ≥ 20 mm Hg; non–structural valve dysfunction (NSVD), defined as severe PPM or ≥ moderate aortic regurgitation; clinical valve thrombosis; endocarditis; and aortic valve reintervention.

Key secondary endpoints included BVD in female patients at 12 months, HSVD in all patients at 12 months, hemodynamic mean gradient (continuous variable) at 12 months, effective orifice area as continuous variable at 12 months, and moderate or severe PPM at 30 days. VARC-3 defined device success at 30 days and the change in Kansas City Cardiomyopathy Questionnaire (KCCQ) ordinal outcome were additional exploratory endpoints.

IMPLICATIONS OF THE SMART TRIAL FOR TREATMENT OF WOMEN

Women present striking differences in clinical outcomes after TAVR as compared to men. Trials conducted in low-surgical-risk AS patients highlighted a potential for better outcomes after TAVR versus SAVR in women.[13-15] In the Transcatheter Valve Therapy registry of the Society of Thoracic Surgeons/American College of Cardiology, encompassing 23,652 patients undergoing TAVR with first-generation THVs, women demonstrated a lower risk of 1-year mortality compared to men (HR, 0.73; 95% CI, 0.63-0.85; $P < .001$), but faced a higher risk of bleeding and access-related complications.[16] These differences in outcomes have partially been attributed to the peculiar clinical characteristics of women undergoing TAVR, including a lower prevalence of atherosclerotic vascular disease, diabetes, and dyslipidemia, along with a higher burden of hypertension, vascular tortuosity, and advanced chronic kidney disease.[17] However, the differences in AS pathophysiology between men and women might also impact TAVR outcomes.[2]

Small aortic annulus is common among patients undergoing TAVR, with an estimated prevalence up to 40%.[2,18] Women constitute up to 90% of the small annulus popula-

	Evolut PRO/PRO+/FX	Sapien 3/Ultra
Annulus Range	17/18-30mm	16-28mm
Valve Placement	Supra-annular	Intra-annular
Frame Material	Nitinol	Cobalt-chromium
Expansion Mechanism	Self-expanding	Balloon-expanding
Tissue Material	Porcine	Bovine
Recapturable	Yes	No
Other Features	Tissue sealing skirt around TAV frame to reduce PVL	Outer PET fabric skirt to reduce PVL

Figure 2. Summary of key differences between the Evolut platform and Sapien platform valves.

tion.[4,19-22] Despite this, few studies have addressed the outcomes of TAVR in small annuli within female populations. In the TAVR-SMALL 2 registry, severe PPM was more frequent in women than in men with small annuli after propensity score matching.[23] In a post hoc analysis of the PARTNER 3 trial, severe PPM emerged as a predictor of the composite of mortality, stroke, and repeat hospitalizations at 1 year in women (HR, 3.67; 95% CI, 1.45-9.32) but not in men (HR, 0.27; 95% CI, 0.04-1.96).[24] Two secondary analyses of the WIN-TAVI (Women's INternational Transcatheter Aortic Valve Implantation) registry, which included 1,019 female patients undergoing TAVR, suggested that both small aortic annulus and PPM had no effect on cardiovascular outcomes at 1-year follow-up.[8,25] However, these secondary analyses from an observational study might have been underpowered to detect significant differences in hard clinical endpoints at short-term follow-up.

On this background, the SMART trial was the first randomized trial, powered for hard clinical endpoints, to evaluate the performance of TAVR with the most contemporary balloon-expandable and self-expanding valve THV devices in women and men with a small aortic annulus.

PERSPECTIVES ON TRIAL RESULTS

A total of 737 patients were randomized, of whom 366 were assigned to receive Evolut and 371 to Sapien THVs. The final implanted population consisted of 350 patients in the Evolut group and 365 in the Sapien group.[26] Importantly, 86.7% of the implanted patients were women.[26]

The first coprimary endpoint, the composite of mortality, disabling stroke, or heart failure hospitalization through 12 months occurred in 9.4% of patients in the Evolut group and in 10.6% of patients in the Sapien group (difference, −1.2%; 90% CI, −4.9 to 2.5; $P < .001$ for noninferiority). The 12-month incidence of the second coprimary endpoint, BVD, was 9.4% in the Evolut group and 41.6% in the Sapien group (difference, −32.2%; 95% CI, −38.7 to −25.6; $P < .001$ for superiority). This was driven by a higher rate of both NSVD (5.9% vs 18.2%; difference, −12.3 percentage points; 95% CI, −17.6 to −7.0) and HSVD (3.2% vs 32.2%, difference, −29.1%; 95% CI, −34.6% to −23.5%; $P < .001$ for superiority) at 12 months in the Sapien group.

The superior performance of the Evolut valve with respect to the BVD endpoint was also consistent when results were assessed in a prespecified analysis of women only, with a 12-month BVD incidence of 8.4% in the Evolut group and 41.8% in the Sapien group (difference, −33.4%; 95% CI, 40.4% to −26.4%; $P < .001$; Figure 3).

CLINICAL IMPLICATIONS AND FUTURE STEPS

The results of the SMART trial are of outmost importance to guide the management of patients with AS and small aortic annulus. Notably, there was a substantial imbalance in BVD incidence, which was fourfold higher and occurred in almost half of patients in the

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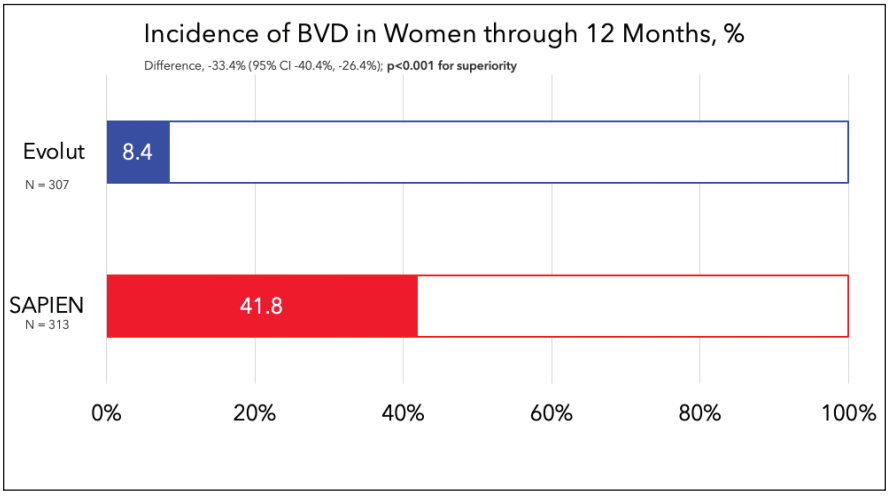

Figure 3. Incidence of BVD in women through 12 months.

Sapien group compared to the Evolut cohort. Although the current 1-year follow-up was too short to unravel differences between the two THV platforms in terms of clinical outcomes, the SMART data should prompt physicians to screen for small aortic annulus and favor the use of a self-expanding THV in such cases.

Beyond its direct clinical implications, the SMART trial was the largest TAVR trial to focus on a female-specific condition by enrolling mostly women at nearly 90%. In 2021, we published the Lancet Women and Cardiovascular Disease commission, which highlighted the underrepresentation of women in contemporary clinical research and advocated for improved enrollment and retention of women in cardiovascular trials.[27] In the TAVR setting, this was partially addressed by the WIN-TAVI, a multinational, prospective, observational registry that included > 1,000 women undergoing TAVR from 2013 to 2015.[14,25] Although initial signals suggesting a greater efficacy of self-expanding THVs compared to balloon-expandable THVs in women emerged from WIN-TAVI, the study's observational design and highly heterogeneous population introduced biases.[28] The SMART trial emphasized a substantial treatment gap between the two device types and underscored the importance of conducting female-specific randomized trials to address unmet clinical needs.

EXECUTIVE SUMMARY

In patients with severe AS and a small aortic annulus—a condition that is highly prevalent in women—TAVR with the self-expanding Evolut PRO/PRO+ THV is noninferior to the balloon-expandable Sapien 3/3 Ultra System for the clinical outcome composite through at 1 year and superior with respect to BVD through 1 year. Although the long-term outcomes are yet to be assessed, the potential impact of BVD on both TAVR durability and mortality should caution against the use of balloon-expandable THVs in TAVR candidates with a small aortic annulus. ■

1. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2023 update: a report from the American Heart Association. Circulation. 2023;147:E93-E621. doi: 10.1161/CIR.0000000000001123
2. Shan Y, Pellikka PA. Aortic stenosis in women. Heart. 2020;106:970-976. doi: 10.1136/heartjnl-2019-315407
3. Buellesfeld L, Stortecky S, Kalesan B, et al. Aortic root dimensions among patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2013;6:72-83. doi: 10.1016/j.jcin.2012.09.007
4. Regazzoli D, Chiarito M, Cannata F, et al. Transcatheter self-expandable valve implantation for aortic stenosis in small aortic annuli: the TAVI-SMALL registry. JACC Cardiovasc Interv. 2020;13:196-206. doi: 10.1016/j.jcin.2019.08.041
5. Ghoneim A, Bouhout I, Demers P, et al. Management of small aortic annulus in the era of sutureless valves: a comparative study among different biological options. J Thorac Cardiovasc Surg. 2016;152:1019-1028. doi: 10.1016/j.jtcvs.2016.06.058
6. Abdelghani M, Mankerious N, Allali A, et al. Bioprosthetic valve performance after transcatheter aortic valve replacement with self-expanding versus balloon-expandable valves in large versus small aortic valve annuli: insights from the CHOICE trial and the CHOICE-Extend registry. JACC Cardiovasc Interv. 2018;11:2507-2518. doi: 10.1016/j.jcin.2018.07.050
7. Herrmann HC, Daneshvar SA, Fonarow GC, et al. Prosthesis-patient mismatch in patients undergoing transcatheter aortic valve replacement: from the STS/ACC TVT registry. J Am Coll Cardiol. 2018;72:2701-2711. doi: 10.1016/j.jacc.2018.09.001
8. Panoulas VF, Chandrasekhar J, Busi G, et al. Prevalence, predictors, and outcomes of patient prosthesis mismatch in women undergoing TAVI for severe aortic stenosis: insights from the WIN-TAVI registry. Catheter Cardiovasc Interv. 2021;97:516-526. doi: 10.1002/ccd.29227
9. Sá MP, Jacquemyn X, Van den Eynde J, et al. Impact of prosthesis-patient mismatch after transcatheter aortic valve replacement: meta-analysis of Kaplan-Meier-derived individual patient data. JACC Cardiovasc Imaging. 2023;16:298-310. doi: 10.1016/j.jcmg.2022.07.013
10. O'Hair D, Yakubov SJ, Grubb KJ, et al. Structural valve deterioration after self-expanding transcatheter or surgical aortic valve implantation in patients at intermediate or high risk. JAMA Cardiol. 2023;8:111-119. doi: 10.1001/jamacardio.2022.4627
11. Rodés-Cabau J, Ribeiro H, Mohammadi S, et al. Transcatheter or surgical aortic valve replacement in patients with severe aortic stenosis and small aortic annulus: a randomized clinical trial. Circulation. 2024 Feb 27;149:644-655. doi: 10.1161/CIRCULATIONAHA.123.067326
12. Herrmann HC, Abdel-Wahab M, Attizzani GF, et al. Rationale and design of the SMall Annuli Randomized To Evolut or SAPIEN Trial (SMART Trial). Am Heart J. 2022;243:92-102. doi: 10.1016/j.ahj.2021.09.011
13. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019;380:1695-1705. doi: 10.1056/NEJMoa1814052
14. Panoulas VF, Francis DP, Ruparelia N, et al. Female-specific survival advantage from transcatheter aortic valve implantation over surgical aortic valve replacement: meta-analysis of the gender subgroups of randomised controlled trials including 3758 patients. Int J Cardiol. 2018;250:66-72. doi: 10.1016/j.ijcard.2017.05.047
15. Blankenberg S, Seiffert M, Vonthein R, et al. Transcatheter or surgical treatment of aortic-valve stenosis. N Engl J Med. Published online April 8, 2024. doi: 10.1056/NEJMoa2400685.
16. Chandrasekhar J, Dangas G, Yu J, et al. Sex-based differences in outcomes with transcatheter aortic valve therapy: TVT Registry from 2011 to 2014. J Am Coll Cardiol. 2016;68:2733-2744. doi: 10.1016/j.jacc.2016.10.041
17. Vlastra W, Chandrasekhar J, García Del Blanco B, et al. Sex differences in transfemoral transcatheter aortic valve replacement. J Am Coll Cardiol. 2019;74:2758-2767. doi: 10.1016/j.jacc.2019.09.015
18. Freitas-Ferraz AB, Tirado-Conte G, Dagenais F, et al. Aortic stenosis and small aortic annulus. Circulation. 2019;139:2685-2702. doi: 10.1161/CIRCULATIONAHA.118.038408
19. Makkar RR, Kapadia S, Chakravarty T, et al. Outcomes of repeat transcatheter aortic valve replacement with balloon-expandable valves: a registry study. Lancet. 2023;402:1529-1540. doi: 10.1016/S0140-6736(23)01636-7
20. Hase H, Yoshijima N, Yanagisawa R, et al. Transcatheter aortic valve replacement with Evolut R versus Sapien 3 in Japanese patients with a small aortic annulus: The OCEAN-TAVI registry. Catheter Cardiovasc Interv. 2021;97:E875-E886. doi: 10.1002/ccd.29259
21. Scotti A, Sturla M, Costa G, et al. Evolut PRO and SAPIEN ULTRA performance in small aortic annuli: The OPERA-TAVI registry. JACC Cardiovasc Interv. 2024;17:681-692. doi: 10.1016/j.jcin.2024.01.006
22. Kalogeras K, Jabbour RJ, Pracon R, et al. Midterm Outcomes in Patients With Aortic Stenosis Treated With Contemporary Balloon-Expandable and Self-Expanding Valves: Does Valve Size Have an Impact on Outcome?. J Am Heart Assoc. 2023;12:e028038. doi: 10.1161/JAHA.122.028038
23. Leone PP, Gohar A, Pagnesi M, et al. Clinical outcomes in women and men with small aortic annuli undergoing transcatheter aortic valve implantation: a multicenter, retrospective, propensity score-matched comparison. Int J Cardiol. 2023;379:16-23. doi: 10.1016/j.ijcard.2023.02.044
24. Pibarot P, Salaun E, Dahou A, et al. Echocardiographic results of transcatheter versus surgical aortic valve replacement in low-risk patients: the PARTNER 3 trial. Circulation. 2020;141:1527-1537. doi: 10.1161/CIRCULATIONAHA.119.044574
25. Pivato CA, Cao D, Spirito A, et al. Impact of small valve size on 1-year outcomes after transcatheter aortic

valve implantation in women (from the WIN-TAVI Registry). Am J Cardiol. 2022;172:73-80. doi: 10.1016/j.amjcard.2022.02.025
26. Herrmann HC, Mehran R, Blackman DJ, et al. Self-expanding or balloon-expandable tavr in patients with a small aortic annulus. N Engl J Med. 2024 Apr 7. doi: 10.1056/NEJMoa2312573. Online ahead of print.
27. Mehran R, Vogel B, Ortega R, et al. The Lancet Commission on women and cardiovascular disease : time for a shift in women's health. Lancet. 2019;393:967-968. doi: 10.1016/S0140-6736(19)30315-0
28. Giannini C, Petronio AS, Mehilli J, et al. Edwards SAPIEN versus Medtronic aortic bioprosthesis in women undergoing transcatheter aortic valve implantation (from the Win-TAVI Registry). Am J Cardiol. 2020;125:441-448. doi: 10.1016/j.amjcard.2019.10.056

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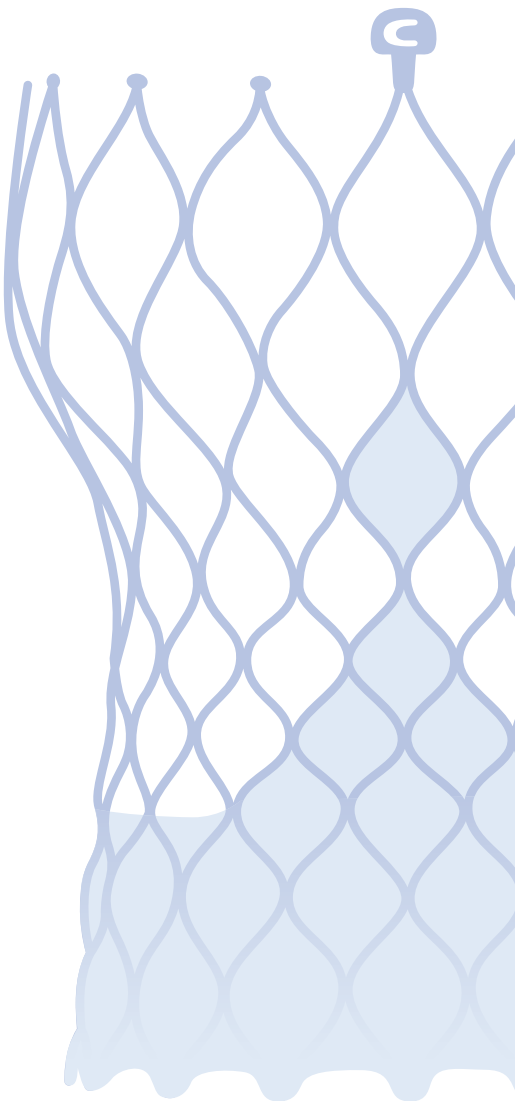

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Indications
The Medtronic CoreValve™ Evolut™ R, Evolut™ PRO+, and Evolut™ FX Systems are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy.

The Medtronic CoreValve Evolut R, Evolut PRO+, and Evolut FX Systems are indicated for use in patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (e.g., STS predicted risk of operative mortality score ≥ 8% or at a ≥ 15% risk of mortality at 30 days).

Contraindications
The CoreValve Evolut R, Evolut PRO+, and Evolut FX Systems are contraindicated in patients who cannot tolerate Nitinol (titanium or nickel), gold (for Evolut FX Systems alone), an anticoagulation/antiplatelet regimen, or who have active bacterial endocarditis or other active infections.

Warnings
General Implantation of the CoreValve Evolut R, Evolut PRO+, and Evolut FX Systems should be performed only by physicians who have received Medtronic CoreValve Evolut R, Evolut PRO+, or Evolut FX training. This procedure should only be performed where emergency aortic valve surgery can be performed promptly. Mechanical failure of the delivery catheter system and/or accessories may result in patient complications. *Transcatheter aortic valve (bioprosthesis)* Accelerated deterioration due to calcific degeneration of the bioprostheses may occur in: children, adolescents, or young adults; patients with altered calcium metabolism (e.g., chronic renal failure or hyperthyroidism).

Precautions
General Clinical long-term durability has not been established for the bioprosthesis. Evaluate bioprosthesis performance as needed during patient follow-up. The safety and effectiveness of the CoreValve Evolut R, Evolut PRO+, and Evolut FX Systems have not been evaluated in the pediatric population. The safety and effectiveness of the bioprostheses for aortic valve replacement have not been evaluated in the following patient populations: Patients who do not meet the criteria for symptomatic severe native aortic stenosis as defined: (1) symptomatic severe high-gradient aortic stenosis – aortic valve area ≤ 1.0 cm^2 or aortic valve area index ≤ 0.6 cm^2/m^2, a mean aortic valve gradient ≥ 40 mm Hg, or a peak aortic-jet velocity ≥ 4.0 m/s; (2) symptomatic severe low-flow, low-gradient aortic stenosis – aortic valve area ≤ 1.0 cm^2 or aortic valve area index ≤ 0.6 cm^2/m^2, a mean aortic valve gradient < 40 mm Hg, and a peak aortic-jet velocity < 4.0 m/s; with untreated, clinically significant coronary artery disease requiring revascularization; with a preexisting prosthetic heart valve with a rigid support structure in either the mitral or pulmonic position if either the preexisting prosthetic heart valve could affect the implantation or function of the bioprosthesis or the implantation of the bioprosthesis could affect the function of the preexisting prosthetic heart valve; patients with liver failure (Child-Pugh Class C); with cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support; patients who are pregnant or breastfeeding. The safety and effectiveness of a CoreValve Evolut R, Evolut PRO+, or Evolut FX bioprosthesis implanted within a failed preexisting transcatheter bioprosthesis have not been demonstrated. Implanting a CoreValve Evolut R, Evolut PRO+, or Evolut FX bioprosthesis in a degenerated surgical bioprosthetic valve (transcatheter aortic valve in surgical aortic valve [TAV-in-SAV]) should be avoided in the following conditions: The degenerated surgical bioprosthetic valve presents with: a significant concomitant paravalvular leak (between the prosthesis and the native annulus), is not securely fixed in the native annulus, or is not structurally intact (e.g., wire form frame fracture); partially detached leaflet that in the aortic position may obstruct a coronary ostium; stent frame with a manufacturer-labeled inner diameter < 17 mm. The safety and effectiveness of the bioprostheses for aortic valve replacement have not been evaluated in patient populations presenting with the following: Blood dyscrasias as defined as leukopenia (WBC < 1,000 cells/mm^3), thrombocytopenia (platelet count < 50,000 cells/mm^3), history of bleeding diathesis or coagulopathy, or hypercoagulable states; congenital unicuspid valve; mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation [3-4+]); moderate to severe (3-4+) or severe (4+) mitral or severe (4+) tricuspid regurgitation; hypertrophic obstructive cardiomyopathy; new or untreated echocardiographic evidence of intracardiac mass, thrombus, or vegetation; native aortic annulus size < 18 mm or > 30 mm per the baseline diagnostic imaging or surgical bioprosthetic aortic annulus size < 17 mm or > 30 mm; transarterial access unable to accommodate an 18 Fr introducer sheath or the 14 Fr equivalent EnVeo InLine™ Sheath when using models ENVEOR-US/D-EVPROP2329US or Evolut FX Delivery Catheter System with InLine™ Sheath when using model D-EVOLUTFX-2329 or transarterial access unable to accommodate a 20 Fr introducer sheath or the 16 Fr equivalent EnVeo InLine Sheath when using model ENVEOR-N-US or transarterial access unable to accommodate a 22 Fr introducer sheath or the 18 Fr equivalent Evolut PRO+ InLine Sheath when using model D-EVPROP34US or Evolut FX Delivery Catheter System with InLine Sheath when using model D-EVOLUTFX-34; prohibitive left ventricular outflow tract calcification; sinus of Valsalva anatomy that would prevent adequate coronary perfusion; significant aortopathy requiring ascending aortic replacement; moderate to severe mitral stenosis; severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20%; symptomatic carotid or vertebral artery disease; and severe basal septal hypertrophy with an outflow gradient.

Before Use Exposure to glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure to the vapors. Damage may result from forceful handling of the catheter. Prevent kinking of the catheter when removing it from the packaging. The bioprosthesis size must be appropriate to fit the patient's anatomy. Proper sizing of the devices is the responsibility of the physician. Refer to the Instructions for Use for available sizes. Failure to implant a device within the sizing matrix could lead to adverse effects such as those listed below. Patients must present with transarterial access vessel diameters of ≥ 5 mm when using models ENVEOR-US/D-EVPROP2329US/D-EVOLUTFX-2329 or ≥ 5.5 mm when using model ENVEOR-N-US or ≥ 6 mm when using models D-EVPROP34US/D-EVOLUTFX-34, or patients must present with an ascending aortic (direct aortic) access site ≥ 60 mm from the basal plane for both systems. Implantation of the bioprosthesis should be avoided in patients with aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) of > 30° for right subclavian/axillary access or > 70° for femoral and left subclavian/axillary access. For subclavian access, patients with a patent left internal mammary artery (LIMA) graft must present with access vessel diameters that are either ≥ 5.5 mm when using models ENVEOR-L-US/D-EVPROP2329US/D-EVOLUTFX-2329 or ≥ 6 mm when using model ENVEOR-N-US or ≥ 6.5 mm when using models D-EVPROP34US/D-EVOLUTFX-34. Use caution when using the subclavian/axillary approach in patients with a patent LIMA graft or patent RIMA graft. For direct aortic access, ensure the access site and trajectory are free of patent RIMA or a preexisting patent RIMA graft. For transfemoral access, use caution in patients who present with multiplanar curvature of the aorta, acute angulation of the aortic arch, an ascending aortic aneurysm, or severe calcification in the aorta and/or vasculature. If ≥ 2 of these factors are present, consider an alternative access route to prevent vascular complications. Limited clinical data are available for transcatheter aortic valve replacement in patients with a congenital bicuspid aortic valve who are deemed to be at low surgical risk. Anatomical characteristics should be considered when using the valve in this population. In addition, patient age should be considered as long-term durability of the valve has not been established.

During Use If a misload is detected during fluoroscopic inspection, do not attempt to reload the bioprosthesis. Discard the entire system. Inflow crown overlap that has not ended before the 4th node within the capsule increases the risk of an infold upon deployment in constrained anatomies, particularly with moderate-severe levels of calcification and/or bicuspid condition. Do not attempt to direct load the valve. After the procedure, administer appropriate antibiotic prophylaxis as needed for patients at risk for prosthetic valve infection and endocarditis. After the procedure, administer anticoagulation and/or antiplatelet therapy per physician/clinical judgment. Excessive contrast media may cause renal failure. Prior to the procedure, measure the patient's creatinine level. During the procedure, monitor contrast media usage. Conduct the procedure under fluoroscopy. Fluoroscopic procedures are associated with the risk of radiation damage to the skin, which may be painful, disfiguring, and long-term. The safety and efficacy of a CoreValve Evolut R, Evolut PRO+, or Evolut FX bioprosthesis implanted within a transcatheter bioprosthesis have not been demonstrated.

Potential adverse events
Potential risks associated with the implantation of the CoreValve Evolut R, Evolut PRO+, or Evolut FX transcatheter aortic valve may include, but are not limited to, the following: • death • myocardial infarction, cardiac arrest, cardiogenic shock, or cardiac tamponade • coronary occlusion, obstruction, or vessel spasm (including acute coronary closure) • cardiovascular injury (including rupture, perforation, tissue erosion, or dissection of vessels, ascending aorta trauma, ventricle, myocardium, or valvular structures that may require intervention) • emergent surgical or transcatheter intervention (e.g., coronary artery bypass, heart valve replacement, valve explant, percutaneous coronary intervention [PCI], balloon valvuloplasty) • prosthetic valve dysfunction (regurgitation or stenosis) due to fracture; bending (out-of-round configuration) of the valve frame; underexpansion of the valve frame; calcification; pannus; leaflet wear, tear, prolapse, or retraction; poor valve coaptation; suture breaks or disruption; leaks; mal-sizing (prosthesis-patient mismatch); malposition (either too high or too low)/malplacement • prosthetic valve migration/embolization • prosthetic valve endocarditis • prosthetic valve thrombosis • delivery catheter system malfunction resulting in the need for additional recrossing of the aortic valve and prolonged procedural time • delivery catheter system component migration/embolization • stroke (ischemic or hemorrhagic), transient ischemic attack (TIA), or other neurological deficits • individual organ (e.g., cardiac, respiratory, renal [including acute kidney failure]) or multi-organ insufficiency or failure • major or minor bleeding that may require transfusion or intervention (including life-threatening or disabling bleeding) • vascular access-related complications (e.g., dissection, perforation, pain, bleeding, hematoma, pseudoaneurysm, irreversible nerve injury, compartment syndrome, arteriovenous fistula, or stenosis) • mitral valve regurgitation or injury • conduction system disturbances (e.g., atrioventricular node block, left bundle-branch block, asystole), which may require a permanent pacemaker • infection (including septicemia) • hypotension or hypertension • hemolysis • peripheral ischemia • General surgical risks applicable to transcatheter aortic valve implantation: • bowel ischemia • abnormal lab values (including electrolyte imbalance) • allergic reaction to antiplatelet agents, contrast medium, or anesthesia • exposure to radiation through fluoroscopy and angiography • permanent disability.

Please reference the CoreValve Evolut R, Evolut PRO+, and Evolut FX Instructions for Use for more information regarding indications, warnings, precautions, and potential adverse events.

Caution: Federal Law (USA) restricts these devices to the sale by or on the order of a physician.

The commercial name of the Evolut™ R device is Medtronic CoreValve™ Evolut™ R System, the commercial name of the Evolut™ PRO+ device is Medtronic Evolut™ PRO+ System, and the commercial name of the Evolut™ FX device is Medtronic Evolut™ FX System.

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