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ORIGINAL RESEARCH

Sex-Associated Disparities in Surgical and Percutaneous Management of Aortic Stenosis With Severe Features: Retrospective Analysis From the National Readmission Database

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BACKGROUND: Referral for valve intervention for severe aortic stenosis (AS) may exhibit sex-associated disparities independent of the growth of transcatheter interventions. This study aimed to determine whether there were sex-associated differences in the use of aortic valve replacement (AVR), either surgical or transcatheter, in patients with aortic stenosis and severe features from a national cohort of patients.

METHODS: Using the National Readmission Database, all patients with an index diagnosis of AS between January 2015 and December 2019 were included and stratified by their 90-day readmission status and sex. AS with severe features was defined as the combination of primary- or secondary-coded diagnosis of AS in combination with heart failure, syncope, angina pectoris, cardiac arrest, or cardiogenic shock. A 1:1 nested case–control matching was performed to account for competing risk. The main investigated outcome was the sex-associated rate of AVR in the 90 days after index hospitalization.

RESULTS: A total of 31 712 matched weighted discharges were included in the analysis, 16 597 men (52.3%) and 15 116 women (47.7%). At 90 days, the rate of AVR was significantly lower in women (45.7% versus 53.6%, $P<0.001$) with significant difference for both surgical ($P<0.001$) and transcatheter ($P=0.010$) interventions. After multivariable adjustment, these differences persisted with women significantly less likely to receive AVR (adjusted odds ratio [aOR], 0.67 [95% CI, 0.63–0.71], $P<0.001$), either surgical AVR (aOR, 0.48 [95% CI, 0.43–0.54], $P<0.001$) or transcatheter aortic valve implantation (aOR, 0.79 [95% CI, 0.75–0.84], $P<0.001$).

CONCLUSIONS: The use of surgical AVR and transcatheter aortic valve implantation was significantly lower in female patients with AS and severe features independent from patient- and hospital-level characteristics.

Key Words: aortic valve replacement ■ disparities ■ sex ■ transcatheter aortic valve intervention

Aortic stenosis (AS) represents an increasing social and economic burden worldwide and poses a relevant future challenge for health care systems.[1,2] Historically, female patients with severe AS have been more frequently rejected for surgical aortic valve replacement (SAVR), mainly because of a greater risk of perioperative complications.[3] The recent insurgence of transcatheter aortic valve implantation (TAVI)

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CLINICAL PERSPECTIVES

What Is New?

- In this nationally-based cohort of weighted discharges with aortic stenosis and severe clinical features, after 1:1 nested case–control matching, we observed a significantly reduced rate of aortic valve replacement in women compared with men, for both surgical and transcatheter valve replacement.

What Are the Clinical Implications?

- The observed sex disparity provides insights for the improvement of the theragnostic workup in patients with aortic stenosis.
- The implementation of sex-specific hemodynamic indexes could potentially improve the prognosis of female patients with symptomatic aortic stenosis allowing a probable more adequate clinical stratification.
- Further educational and political efforts must be made at a national level to tailor diagnostic workup in the case of female patients with symptomatic aortic stenosis and deliver the appropriate intervention.

Nonstandard Abbreviations and Acronyms

AS	aortic stenosis
AVR	aortic valve replacement
NRD	National Readmission Database
SAVR	surgical aortic valve replacement
TAVI	transcatheter aortic valve implantation

has allowed improved therapeutic delivery to a broader population, representing an important treatment paradigm shift.[4]

Both European and US guidelines for the management of valvular heart diseases give a class Ia recommendation for intervention in adults with documented severe AS and symptoms of dyspnea, heart failure, angina, and syncope.[5,6] Nevertheless, emerging evidence suggests continued disparities in the use of treatment strategies between male and female patients.[7–12] Although much of the previous literature has focused on the imbalance in the prevalence of men and women treated with TAVR, it is not clear whether such differences are merely a reflection of sex-related differences in the indication for aortic interventions or related to systematic disparities in referral for those with an indication for intervention. Different underlying mechanisms have been previously outlined to explain such management disparities. On one hand, advanced age at presentation, lower body surface area, and smaller vessels portend women at higher risk for procedural bleeding and vascular complications.[13] On the other hand, several studies have highlighted the potential underreferral of female patients compared with male patients indicating potential sex-related barriers to treatment provision[7] despite proven favorable outcomes.[14] Yet, the literature lacks robust contemporary data in this field to determine the existence of sex-associated referral disparities in the real-world population with severe symptomatic AS.

Therefore, this study aimed to investigate a nationally representative population-based sample for the presence of actual sex-associated disparities in referral to AVR therapy, either surgical or transcatheter, in patients with AS hospitalized with guideline-recommended indications to intervention.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. The analysis uses anonymized data. Ethical approval and consent were not required.

The Nationwide Readmission Database (NRD) is a publicly available anonymized data set produced by the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project. The NRD is designed to accommodate analyses of national readmission rates for all the payers and insured individuals in the United States. It is drawn from Healthcare Cost and Utilization Project State Inpatient Databases that contain verified patient linkage numbers that can be used to track a patient across hospitals within a state, within a calendar year. Each year is independent and there are no linkages across years. The NRD accounts for about 61.2% of the total US resident population and 59.6% of all US hospitalizations (unweighted discharges). Discharge weights are then calculated using poststratification on hospital and patient characteristics and applied to the unweighted data, allowing the estimate of the number of discharges for the target NRD universe.[15]

This study enrolled a sample of case controls of adult patients with AS and severe features in the NRD between January 2015 and December 2019. Using the *International Classification of Diseases, Tenth Revision* (*ICD-10*), AS with guideline-recommended indication to intervention was defined as the primary- or secondary-coded diagnosis of AS (I35.0, I35.2, I06.0, I06.2) in combination with the primary- or secondary-coded diagnosis of congestive heart failure (*ICD-10*: I110, I130, I132, I0981, I50, I50.1, I50.20, I50.21, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.43, I50.8, I50.81, I50.810, I50.811, I50.812, I50.813, I50.814, I50.82, I50.83, I50.84, I50.89, I50.9), syncope (R55), angina pectoris (I20.8, I20.9, R072, R078.9, R09, I20.0), cardiac arrest (I46, I46.2, I46.8, I46.9), or cardiogenic shock (R57.0). Exclusion criteria were index discharge between October to December (n=45 543 weighted cases), elective index admission (n=4708 weighted cases), age <18 years (n=38 weighted cases), history of prior valve replacement or combined valve surgery (n=8340 weighted cases), and SAVR or TAVI during index admission (n=1176 weighted discharges). Patients with missing data regarding age, sex, in-hospital death, length of stay, expected primary payer, and total charges at discharge (n=865 weighted cases) were also excluded. AVR was defined according to the relative *ICD-10 Procedure Coding System* (*ICD-10-PCS*) as either SAVR (02RF07Z, 02RF08Z, 02RF0JZ, 02RF0KZ) or TAVI (02RF37H, 02RF37Z, 02RF38H, 02RF38Z, 03RF38Z, 02RF3jH, 02RF3JZ, 02RF3KH, 02RF3KZ).

Costs for admissions and readmissions were estimated by considering the total charge multiplied by the charge-to-cost ratio as per Healthcare Cost and Utilization Project recommendations. Patient demographics, comorbidities, hospital characteristics, and other inpatient variables were derived from data sets available in the NRD, Agency for Healthcare Research and Quality comorbidity measure and *ICD-10* diagnosis and procedure codes as described in Table S1.

The primary outcome of this study was the sex-associated rates of AVR in the 90 days after index hospitalization. Secondary outcome was the sex-associated in-hospital mortality rates in patients receiving AVR in the 90 days after index hospitalization.

All statistical analyses were performed using SPSS version 26 (IBM Corp, Armonk, NY), STATA version 14 (StataCorp LLC, College Station, TX) and GraphPad Prism version 9.0.0 (GraphPad Software, Boston, MA). To address potential competing risks and selection bias,[16,17] we implemented a standard nested case–control matching analysis with a 1:1 ratio using the SPSS algorithm. The study population was defined as cases presenting with severe AS features at the time of index admission. From this cohort, we identified cases who underwent AVR within 90 days and matched them randomly (1:1) with controls who were readmitted within the same 90-day period but did not receive AVR. This matching was performed through SPSS using the standard case–control matching command (fuzzy matching variable with "0" match tolerance=90-day readmissions; demander/supplier indicator variable=90-day AVR). In addition, we stratified the sample by sex to explore potential sex-related differences in outcomes. Using this algorithmic approach (Figure 1), the balanced sample of 1:1 matched cases receiving and not receiving AVR at 90 days was defined.

Statistical Analysis

Continuous variables were summarized using median and interquartile range (IQR) and compared using the Mann–Whitney *U* test. Categorical variables were summarized as percentages (%) and compared using the chi-square test. Multivariable conditional logistic regression was performed to determine the respective adjusted odds ratios (aOR) with 95% CI for AVR, SAVR, and TAVI in the matched cohorts. The variables included in the models were a priori determined based on their clinical relevance. The logistic regression models were adjusted for the following variables: age, primary expected payer, median household income, residency same state admission hospital, hospital bed size, region and teaching status, length of stay, diabetes, hypertension, obesity, chronic lung disease, arrhythmias, chronic liver disease, solid cancer, peripheral vascular disease, renal failure, prior percutaneous coronary intervention, prior coronary artery bypass grafting, prior myocardial infarction, primary index diagnosis angina, primary index diagnosis heart failure, and primary index diagnosis syncope. Results were determined significant at the level of $P<0.05$.

RESULTS

From the 114 351 118 weighted discharges with AS extracted from the NRD, after application of exclusion and criteria, a total of 207 486 cases with AS with severe features were initially screened. Nested 1:1 case–control matching was performed as previously illustrated and a total of 31 712 matched weighted discharges with readmission within 90 days were included in the final analysis (Figure 2).

The median age of the global cohort was 81 years (IQR, 74–88 years) with 72.5% being ≥75 years old. Among this cohort, 16 597 (52.3%) were male and 15 116 (47.7%) were female. When looking at the primary-coded principal admission diagnoses, heart failure was the most frequent (71%), followed by aortic stenosis (24.9%), syncope (2.2%), and angina (1.8%). The most frequent associated clinical conditions were arrhythmias (55.0%) and renal failure (48.2%) and hypertension, chronic pulmonary disease, and obesity were the most prevalent associated comorbidities (91.1%, 34.8%, and 20.6%, respectively).

Patient- and hospital-level characteristics at index admission were distinctly different between sexes, as shown in Tables 1 and 2 and Figure S1. Female patients were significantly older than male patients (median age: 83; IQR, 75–89 years versus 80, IQR, 72–87 years; $P<0.001$) with a higher proportion of patients aged ≥75 years (77.8% versus 67.7%, $P<0.001$). Arrhythmias and renal failure were significantly more prevalent in men (75.2% versus 52.6%, $P<0.001$; 51.5%

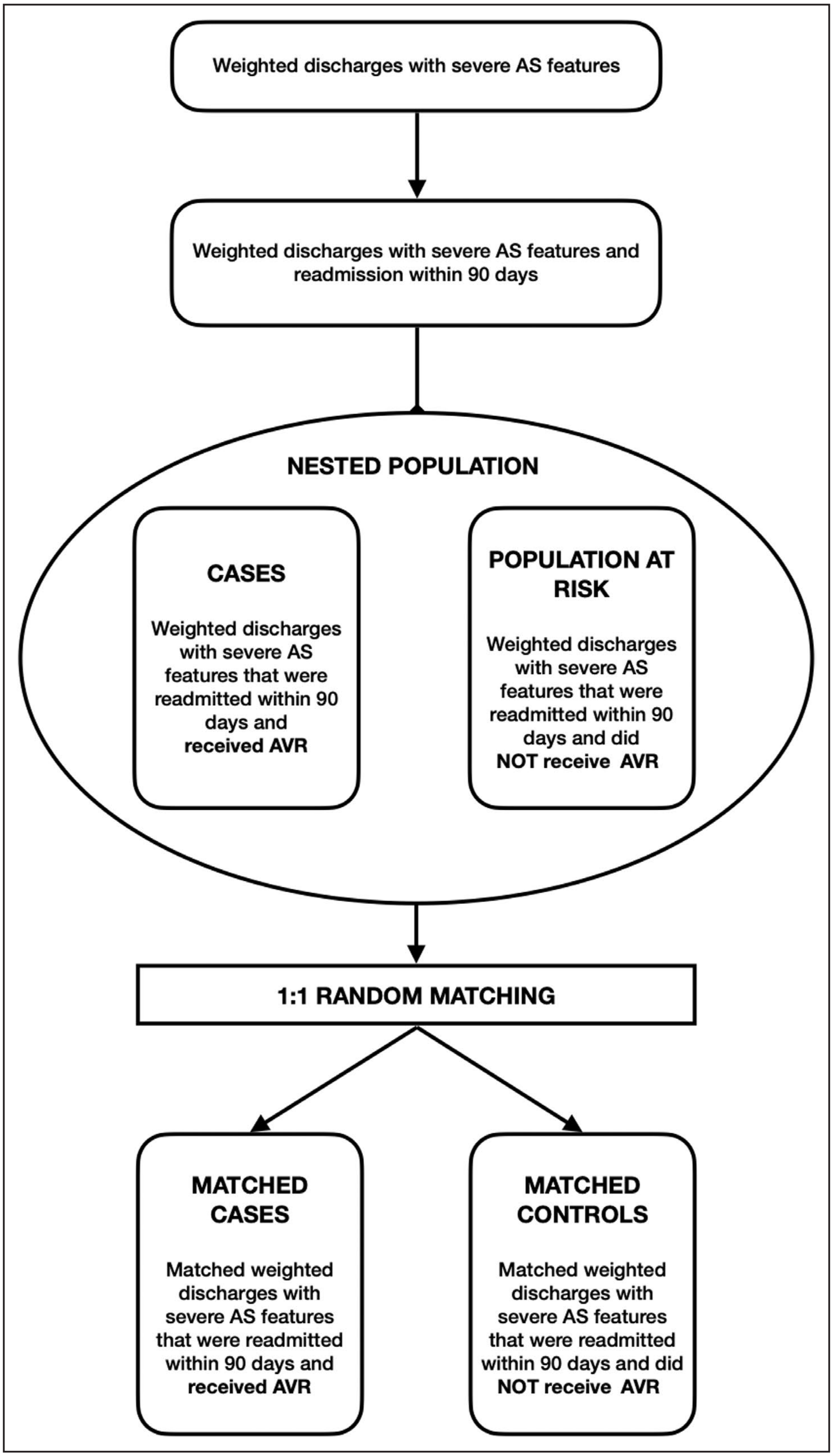

Figure 1. Graphical illustration of the nested case–control 1:1 matching algorithm.
AS indicates aortic stenosis; and AVR, aortic valve replacement.

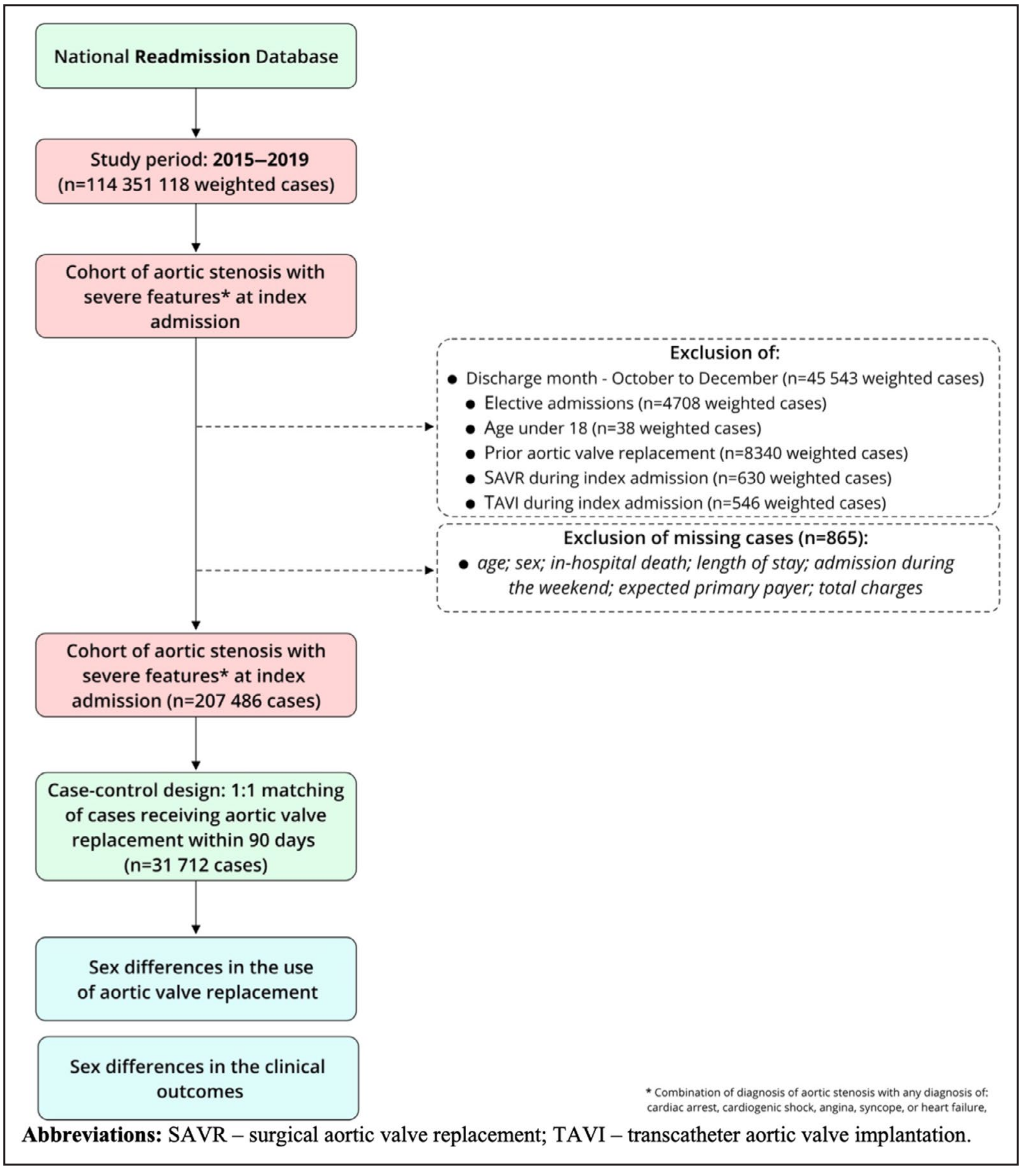

Figure 2. Flow diagram of the study.
SAVR indicates surgical aortic valve replacement; and TAVI, transcatheter aortic valve implantation.

versus 44.6%, *P*<0.001) whereas obesity (22.1% versus 19.2%, *P*<0.001), anemia (9.9% versus 8.4%, *P*<0.001), and depression (13.0% versus 7.9%, *P*<0.001) were more prevalent in women. More frequently, male patients had a previous history of coronary artery bypass grafting (19.9% versus 8.7%, *P*<0.001), myocardial infarction (15.7% versus 9.9%, *P*<0.001), and percutaneous coronary intervention (2.0% versus 1.5%, *P*<0.001).

At 90 days, 50.0% of patients received AVR: 10.3% SAVR and 39.7% TAVI. Men were significantly more likely to receive AVR (53.6% versus 45.7%, *P*<0.001) than women, either SAVR (13.3% versus 6.9%, *P*<0.001) or TAVI (40.3% versus 38.8%, *P*=0.010) (Table 3). Stratifying weighted discharges according to AVR status (Table 4), patients who received AVR in the 90 days after index admission were younger (median age 80, IQR, 72–86 years versus 83, IQR, 75–89 years, *P*<0.001) with a less severe clinical presentation and lower risk of in-hospital mortality, described by higher All Patient Refined-Diagnosis Related Group scores (extreme severity of illness: 11.6% versus 14.5%, *P*<0.001; extreme risk of mortality: 14.2% versus 18.8%, *P*<0.001) with lower prevalence of arrhythmias (50.0% versus 59.9%, *P*<0.002) and renal failure (40.3% versus 56.1%, *P*<0.001). Moreover, patients receiving AVR were more likely hospitalized in large and teaching hospitals (large bed size of hospital 62.0% versus 48.4%, *P*<0.001; teaching status 76.4% versus 63.9%, *P*<0.001). Finally, in the multivariate logistic model, female sex was a variable independently associated with

Table 1. Baseline and Hospital-Level Characteristics at Index Admission of Patients With Severe AS Features, According to Sex

Characteristics	Full selected cohort (100.0%)	Male sex (52.3%)	Female sex (47.7%)	*P* value*
Number of weighted discharges	31 712	16 597	15 116	…
Age (y), median (IQR)	81 (74–88)	80 (72–87)	83 (75–89)	<0.001†
Age categories (y)				<0.001†
<65	10.1	14.0	8.0	…
65–74	16.3	18.3	14.2	…
≥75	72.5	67.7	77.8	…
Primary expected payer (%)				<0.001†
Medicare	88.7	85.9	91.7	…
Medicaid	2.5	2.7	2.2	…
Private insurance	6.8	8.2	5.2	…
Self-pay	0.7	0.9	0.4	…
Other	1.4	2.2	0.5	…
Median household income quartiles (%)				0.001†
0–25th	24.7	24.1	25.3	…
26th–50th	27.7	27.6	27.7	…
51st–75th	25.6	25.4	25.9	…
76th–100th	22.0	22.9	21.1	…
Resident in hospital state, %	94.5	94.0	95.0	<0.001†
Weekend admission, %	23.2	22.8	23.7	0.056
APR-DRG: severity of illness, %				<0.001†
Minor	6.1	6.1	6.0	…
Moderate	34.0	34.2	33.9	…
Major	46.9	47.6	46.0	…
Extreme	13.0	12.1	14.1	…
APR-DRG: risk of mortality, %				<0.001†
Minor	4.4	4.9	3.9	…
Moderate	32.2	32.1	32.3	…
Major	46.9	47.4	46.4	…
Extreme	16.5	15.6	17.4	…
Associated conditions and comorbidities, %				
Arrhythmias	55.0	57.2	52.6	<0.001†
Renal failure	48.2	51.5	44.6	<0.001†
Obesity	20.6	19.2	22.1	<0.001†
Arterial hypertension	91.1	90.6	91.8	<0.001†
Diabetes	16.3	16.3	16.3	0.995
Peripheral vascular disease	15.1	16.9	13.1	<0.001†
Previous myocardial infarction	12.9	15.7	9.9	<0.001†
Previous PCI	1.8	2.0	1.5	0.001†
Previous CABG	14.5	19.9	8.7	<0.001†
Anemia	9.1	8.4	9.9	<0.001†
Chronic pulmonary disease	34.8	34.6	35.1	0.299
Coagulopathy	6.4	7.5	5.1	<0.001†
Chronic liver disease	3.3	3.9	2.8	<0.001†
Neurologic disorder	3.2	3.6	2.7	0.002†
Solid cancer	2.7	3.1	2.4	<0.001†
Metastatic cancer	0.9	0.9	0.8	0.159†
Depression	10.4	7.9	13.0	<0.001†

(*Continued*)

Table 1. Continued

Characteristics	Full selected cohort (100.0%)	Male sex (52.3%)	Female sex (47.7%)	*P* value*
Procedures during index hospitalization, %				
PCI	4.7	5.4	3.9	<0.001†
CABG	0.1	0.1	<0.1	0.091
Permanent pacemaker	1.1	1.1	1.0	0.340
Bed size of hospital, %				0.601
Small	16.5	16.2	16.8	…
Medium	28.3	28.1	28.6	…
Large	55.2	55.7	54.6	…
Teaching hospital, %	70.1	70.6	69.7	0.096
Hospital location, %				<0.001†
Large urban metropolitan	55.8	55.4	56.2	…
Small metropolitan	36.8	37.4	36.1	…
Micropolitan or nonmetropolitan	7.4	7.1	7.7	…
Length of index hospital stay, d, median (IQR)	4 (2–6)	4 (2–6)	4 (3–7)	
Hospital ownership, %				<0.001†
Government, nonfederal	8.5	9.1	7.9	…
Private, nonprofit	78.7	78.6	78.8	…
Private, invest-own	12.8	12.3	13.2	…
Total costs, US dollars, median (IQR)	9674 (5750–16322)	9977 (5688–16832)	9402 (5807–15812)	<0.001†

APR-DRG indicates all patient refined-diagnosis related group; AS, aortic stenosis; CABG, coronary artery bypass graft; IQR, interquartile range; and PCI, percutaneous coronary intervention.
*Comparison between male and female patients.
†$P<0.05$.

less probability of receiving AVR (aOR, 0.67 [95% CI, 0.63–0.71], *P*<0.001), SAVR (aOR, 0.48 [95% CI, 0.43–0.54], *P*<0.001) and TAVI (aOR, 0.79 [95% CI, 0.75–0.84], *P*<0.001) (Tables 5, 6 and 7, Figure 3).

The in-hospital mortality rates in patients who underwent AVR within the 90 days after index admission were similar between sexes (male 4.3% versus female 4.6%, *P*=0.397). However, the in-hospital mortality rate in patients was significantly higher in women compared with men in case of SAVR (6.8% versus 4.8%, *P*=0.023) but not in the case of TAVI (4.3% versus 4.2%) (Table S2)

DISCUSSION

This national-level study reports important contemporary data on sex-associated differences in guideline-recommended intervention for AS. Two important findings of this study should be pointed out. First, female patients with AS and severe features receive significantly fewer AVRs, either surgical or transcatheter, up to 90 days after index admission irrespective of patient- and hospital-level characteristics. Second, compared with men the 90-day in-hospital mortality of female patients was significantly higher in those who underwent SAVR but not in those who underwent TAVI. In comparison with previous studies that focused on a posteriori differences in outcomes between sexes after AVR, either SAVR or TAVI, this is the first study to date that directly addresses the potential presence of a priori disparities between sexes in referral to AVR in patients with AS and severe features.

The relationship between female sex and use of SAVR and TAVI is controversial[18] and is mostly derived from subgroup analyses of large trials.[19–21] These trials do not provide insights into whether women are at a disadvantage in receiving treatment for severe AS. Thus, further real-world studies are necessary to provide insights into sex disparities in referrals for AS.

Female sex per se is an important component of most perioperative risk scores in cardiac surgery.[22–25] However, how and to what extent sex should weigh on the decision-making process when choosing AVR options has long been debated.[26] Despite some inherent anatomical characteristics that can potentially affect mid- and long-term prognosis (eg, smaller average aortic annulus), the differences in short-term mortality associated with SAVR[8,27,28] have been shown to be related not to sex itself but to the older age of presentation and the different preoperative risk profiles women present at the time of surgery (eg, diabetes, hypertension, congestive heart failure, etc.).[29,30] In some cases, this might lead to female patients being assessed as having a higher risk, potentially influencing

Table 2. Principal Admission Causes at Index Admission of Patients With Severe AS Features According to Sex

Primary discharge diagnosis at index admissions	Full selected cohort (100.0%)	Male sex (52.3%)	Female sex (47.7%)	*P* value*
Number of weighted discharges	31 712	16 597	15 116	…
Aortic stenosis	24.9	26.0	23.8	<0.001†
Heart failure	71.0	70.0	72.1	<0.001†
Syncope	2.2	2.3	2.2	0.829
Angina pectoris	1.8	1.7	1.9	0.157
Cardiac arrest	<0.1	0.1	<0.1	0.032†
Cardiogenic shock	<0.1	<0.1	<0.1	0.482

AS indicates aortic stenosis.
*Comparison between male and female patients.
†$P<0.05$.

the decision to proceed with surgery. Therefore, use of validated risk stratification tools to calculate objective measures of risk and a multidisciplinary approach to valvular disease is crucial. All patients considered for valve intervention should be evaluated by a heart team, which represents a cornerstone element of the clinical decision-making process in both US and European guidelines for the management of valvular diseases.[5,6] Notably, short-term mortality in TAVI did not appear to be significantly different between the sexes in all the largest trials involving symptomatic AS with intermediate-high surgical risk, potentially neutralizing, and to some extent even reversing, the sex disparity in short-term mortality seen with SAVR.[26] However, in our analysis, we showed that in an all-comers national-representative cohort, despite correction for multiple clinical variables and irrespective of the modality of intervention, either surgical or transcatheter, women received significantly fewer AVRs than men. Hence, other factors beyond baseline clinical risk profile must play a role in this sex disparity.

Progression of AS shows different patterns between sexes with profound differences in anatomical macro- and microstructural architecture: at equal Doppler-derived gradients women tend to develop lower degrees of aortic valve calcification but thicker and more fibrotic left ventricular with smaller cavities compared with men, who, on the contrary, tend to develop dilated cardiomyopathy with progressive systolic dysfunction.[9,13,31,32] Thus, the different left ventricular adaptive remodeling can lead to more pronounced symptoms even with lower pressure gradients contributing to later treatment in women and consequent reduced survival probability at follow-up.[9,33] A multiparametric and comprehensive echocardiographic multiwindow approach, coupled with an appropriate use of multimodality imaging, is therefore even more important in women[34]: Bienjonetti-Boudreau et al. have previously shown that female patients with AS more frequently presented with discordant low-gradient phenotype (mean gradient <40 mmHg and indexed calculated area <0.6 cm^2/m^2) and that this group showed a statistical significant adjusted higher mortality at 1 year in women especially when initially nontreated.[35] Therefore, in female patients with symptomatic AS it is even more important for a comprehensive multiwindow echocardiographic assessment to appropriately define hemodynamics, flow status, and ventricular-arterial coupling (eg, systematic implementation of right parasternal axis, flow rate, and valvulo-arterial impedance assessment in case of discordant elements).[36–38] In case of persistent discordance between these measurements, then dobutamine stress echo to ascertain flow status and contractile reserve can be performed[5] as well as other noninvasive imaging modalities such as computed tomography and

Table 3. Receipt of Surgical or Percutaneous Aortic Valve Intervention (SAVR or TAVI) of Patients With Severe AS Features According to Sex

Outcomes	Full selected cohort (100.0%)	Male sex (52.3%)	Female sex (47.7%)	*P* value*
Number of weighted discharges	31 712	16 597	15 116	…
AVR at 90 d, %	50.0	53.6	45.7	<0.001†
SAVR, %	10.3	13.3	6.9	<0.001†
TAVI, %	39.7	40.3	38.8	0.010†

AS indicates aortic stenosis; AVR, aortic valve replacement; SAVR, surgical aortic valve replacement; and TAVI, transcatheter aortic valve implantation.
*Comparison between male and female patients.
†$P<0.05$.

Table 4. Baseline and Hospital-Level Characteristics at Index Admission of Patients With Severe AS Features According to AVR Use at 90 Days and Sex

Characteristics	All readmitted patients not receiving AVR (50.0%)	All readmitted patients receiving AVR (50.0%)	*P* value*	Male pts not receiving AVR (46.4%)	Male pts receiving AVR (53.6%)	*P* value†	Female pts not receiving AVR (54.3%)	Female pts receiving AVR (45.7%)	*P* value‡
Number of weighted discharges	15 902	15 810	…	7701	8896	…	8201	6914	…
Age, y, median (IQR)	83 (75–89)	80 (72–86)	<0.001§	81 (74–88)	79 (71–85)	<0.001§	85 (77–90)	81 (73–86)	<0.001§
Age categories, y			<0.001§			<0.001§			<0.001§
<65	8.6	13.8	…	10.5	7.0	…	6.7	8.6	…
65–74	14.2	18.4	…	16.6	19.8	…	12.0	16.7	…
≥75	77.2	67.8	…	72.9	63.2	…	81.3	73.7	…
Primary expected payer, %			<0.001§			<0.001§			<0.001§
Medicare	91.2	86.1	…	88.9	83.4	…	93.3	89.7	…
Medicaid	2.3	2.7	…	2.5	2.9	…	2.1	2.4	…
Private insurance	4.9	8.6	…	6.0	10.2	…	4.0	6.6	…
Self-pay	0.4	0.9	…	0.7	1.1	…	0.2	0.6	…
Other	1.1	1.7	…	1.9	2.5	…	0.4	0.7	…
Median household income quartiles (%)			<0.001§			<0.001§			0.001§
0–25th	26.0	23.3	…	25.8	22.7	…	26.2	24.2	…
26th–50th	27.8	27.6	…	27.5	27.7	…	28.0	27.3	…
51st–75th	25.1	26.2	…	24.4	26.3	…	25.7	26.0	…
76th–100th	21.1	23.0	…	22.3	23.4	…	20.1	22.4	…
Resident in hospital state, %	96.3	92.7	<0.001§	95.6	92.6	<0.001§	96.9	92.9	<0.001§
Weekend admission, %	24.6	21.8	<0.001§	23.6	22.1	<0.001§	25.6	21.4	<0.001§
APR-DRG: severity of illness (%)			<0.001§						
Minor	5.3	6.9	…	5.0	7.0	…	5.5	6.6	…
Moderate	31.0	37.0	…	31.2	36.7	…	30.9	37.4	…
Major	49.1	44.6	…	50.1	45.5	…	48.2	43.4	…
Extreme	14.5	11.6	…	13.7	10.8	…	15.3	12.6	…
APR-DRG: risk of mortality, %			<0.001§			<0.001§			<0.001§
Minor	2.4	6.4	…	2.6	6.8	…	2.3	5.8	…
Moderate	29.8	34.7	…	29.8	34.2	…	29.8	35.3	…
Major	49.0	44.8	…	49.5	45.5	…	48.5	43.9	…
Extreme	18.8	14.2	…	18.1	13.5	…	19.5	15.0	…

(Continued)

Table 4. Continued

Characteristics	All readmitted patients not receiving AVR (50.0%)	All readmitted patients receiving AVR (50.0%)	*P* value*	Male pts not receiving AVR (46.4%)	Male pts receiving AVR (53.6%)	*P* value†	Female pts not receiving AVR (54.3%)	Female pts receiving AVR (45.7%)	*P* value‡
Associated conditions and comorbidities (%)									
Arrhythmias	59.9	50.0	<0.001§	62.6	52.6	<0.001§	57.5	46.8	<0.001§
Renal failure	56.1	40.3	<0.001§	60.1	44.1	<0.001§	52.4	35.4	<0.001§
Obesity	19.3	21.9	<0.001§	17.4	20.7	<0.001§	21.0	23.4	0.001§
Arterial hypertension	92.3	90.0	<0.001§	91.7	89.6	<0.001§	92.8	90.5	<0.001§
Diabetes	14.4	18.2	<0.001§	14.1	18.2	<0.001§	14.6	18.3	<0.001§
Peripheral vascular disease	13.9	16.3	<0.001§	16.2	17.5	0.026§	11.7	14.7	<0.001§
Previous myocardial infarction	14.4	11.4	<0.001§	17.4	14.3	<0.001§	11.7	7.8	<0.001§
Previous PCI	1.6	1.9	0.047§	1.9	2.1	0.243	1.4	1.6	0.172
Previous CABG	16.4	12.7	<0.001§	23.0	17.2	<0.001§	10.2	6.8	<0.001§
Anemia	9.7	8.0	<0.001§	9.2	7.1	<0.001§	10.1	9.2	0.135
Chronic pulmonary disease	39.0	30.7	<0.001§	39.1	30.7	<0.001§	38.9	30.7	<0.001§
Coagulopathy	6.7	6.0	0.005§	8.2	6.9	0.001§	5.3	4.8	0.168
Chronic liver disease	3.5	3.2	0.135	4.4	3.4	<0.001§	2.6	2.9	0.243
Neurologic disorder	3.8	2.6	<0.001§	4.4	2.9	0.003§	3.3	2.1	0.001§
Solid cancer	3.2	2.3	<0.001§	3.8	2.5	<0.001§	2.6	2.1	0.065
Metastatic cancer	1.2	0.5	<0.001§	1.4	0.5	<0.001§	1.0	0.6	0.008§
Depression	11.4	9.4	<0.001§	9.4	6.7	<0.001§	13.2	12.8	0.390
Procedures during index hospitalization, %									
PCI	1.9	7.5	<0.001§	2.5	8.0	<0.001§	1.3	6.9	<0.001§
CABG	0.1	<0.1	0.005§	0.2	<0.1	0.003§	<0.1	<0.1	0.542
Permanent pacemaker	0.7	1.5	<0.001§	0.7	1.5	<0.001§	0.6	1.4	0.429
Bed size of hospital (%)			<0.001§			<0.001§			<0.001§
Small	20.8	12.2	…	20.4	12.6	…	21.2	11.7	…
Medium	30.8	25.7	…	30.4	26.0	…	31.2	25.4	…
Large	48.4	62.0	…	49.2	61.4	…	47.6	62.9	…
Teaching hospital, %	63.9	76.4	<0.001§	63.8	76.4	<0.001§	64.1	76.4	<0.001§
Hospital location, %			<0.001§			<0.001§			<0.001§
Large urban metropolitan	54.2	57.4	…	53.5	57.1	…	54.8	57.9	…

(*Continued*)

Table 4. Continued

Characteristics	All readmitted patients not receiving AVR (50.0%)	All readmitted patients receiving AVR (50.0%)	*P* value*	Male pts not receiving AVR (46.4%)	Male pts receiving AVR (53.6%)	*P* value†	Female pts not receiving AVR (54.3%)	Female pts receiving AVR (45.7%)	*P* value‡
Small metropolitan	35.5	38.1	…	36.2	38.5	…	34.9	37.6	…
Micropolitan or nonmetropolitan	10.4	4.4	…	10.2	4.4	…	10.4	4.6	…
Length of index hospital stay, d, median (IQR)	4 (3–6)	4 (2–7)	0.001§	4 (3–6)	4 (2–7)	<0.001§	4 (3–6)	4 (2–7)	0.593
Hospital ownership, %			<0.001§			<0.001§			<0.001§
Government, nonfederal	8.9	8.1	…	9.3	8.8	…	8.6	7.2	…
Private, nonprofit	77.2	80.3	…	77.1	79.9	…	77.3	80.7	…
Private, invest-own	13.9	11.6	…	13.5	11.3	…	14.2	12.1	…
Total costs, US dollars, median (IQR)	8157 (5334-12 973)	12 053 (6809-19 845)	<0.001§	8330 (5282–12 244)	11 890 (6553–20 126)	<0.001§	8030 (5368–12 490)	12 126 (7098–19 701)	<0.001§

APR-DRG indicates all patient refined-diagnosis related group; AS, aortic stenosis; AVR, aortic valve replacement; CABG, coronary artery bypass graft; IQR, interquartile range; and PCI, percutaneous coronary intervention.

*Comparison between all readmitted patients not receiving AVR and all readmitted patients receiving AVR.

†Comparison between male patients not receiving AVR and male patients receiving AVR.

‡Comparison between female patients not receiving AVR and female patients receiving AVR.

§$P<0.05$.

Table 5. Conditional Logistic Multivariable Model with Adjusted Odds Ratio and 95% CI for Aortic Valve Replacement, Either Surgical or Percutaneous, in Readmitted Patients With Severe AS Features, After 1:1 Matching

Variables	AVR	
	aOR (95% CI)	*P* value
Female sex	0.67 (0.63–0.71)	<0.001†
Age	0.97 (0.96–0.97)	<0.001†
Hospital bed size*		
Medium	1.22 (1.13–1.34)	<0.001†
Large	1.57 (1.45–1.70)	<0.001†
Length of stay	1.00 (0.99–1.01)	0.476
Primary expected payer*		
Medicaid	1.09 (0.96–1.22)	0.186
Private insurance	0.81 (0.55–1.17)	0.256
Resident in same hospital state	0.76 (0.66–0.88)	<0.001†
Median household income (highest quartile)*	1.37 (1.26–1.49)	<0.001†
Hospital teaching status*	1.22 (1.14–1.31)	<0.001†
Diabetes	1.08 (1.00–1.17)	0.047†
Hypertension	0.99 (0.89–1.01)	0.770
Anemia	0.87 (0.79–0.96)	<0.001†
Renal failure	0.58 (0.55–0.62)	<0.001†
Arrhythmias	0.73 (0.69–0.77)	<0.001†
Chronic pulmonary disease	0.68 (0.64–0.72)	<0.001†
Liver disease	0.63 (0.54–0.75)	<0.001†
Solid cancer	0.67 (0.56–0.79)	<0.001†
Peripheral vessel disease	1.17 (1.08–1.27)	<0.001†
Prior myocardial infarction	0.76 (0.69–0.83)	<0.001†
Prior PCI	0.97 (0.77–1.22)	0.803
Prior CABG	0.78 (0.72–0.85)	<0.001†

The following variables have been included in the logistic regression models: age, sex, primary expected payer, median household income, residency in same state as admission hospital, hospital bed size, hospital teaching status, length of stay, diabetes, hypertension, anemia, chronic lung disease, arrhythmias, chronic liver disease, solid cancer, peripheral vascular disease, renal failure, prior PCI, prior CABG, and prior myocardial infarction. aOR indicates adjusted odds ratio; AS, aortic stenosis; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; and PCI, percutaneous coronary intervention.

*Reference groups are "small hospital bed size" (hospital bed size category), "Medicare" (primary expected payer category), "lowest quartile" (median household income category), and "nonteaching hospitals"' (hospital teaching status category).

†$P<0.05$.

Table 6. Conditional Logistic Multivariate Model With Adjusted Odds Ratio and 95% CI for Surgical Aortic Valve Replacement, in Readmitted Patients With Severe AS Features, After 1:1 Matching

Variables	SAVR	
	aOR (95% CI)	*P* value
Female sex	0.48 (0.43–0.54)	<0.001†
Age	0.91 (0.90–0.91)	<0.001†
Hospital bed size*	…	…
Medium	1.03 (0.88–1.22)	0.688
Large	1.04 (0.89–1.21)	0.610
Length of stay	0.95 (0.93–0.97)	<0.001†
Primary expected payer*	…	…
Medicaid	0.83 (0.64–1.07)	0.151
Private insurance	1.58 (1.33–1.89)	<0.001†
Resident in same hospital state	0.91 (0.68–1.20)	0.498
Median household income (highest quartile)*	1.24 (1.05–1.48)	0.014†
Hospital teaching status*	0.88 (0.77–1.00)	0.059
Diabetes	1.22 (1.06–1.41)	<0.001†
Hypertension	1.04 (0.87–1.24)	0.657
Anemia	0.76 (0.60–0.97)	0.025†
Renal failure	0.40 (0.35–0.45)	<0.001†
Arrhythmias	0.69 (0.62–0.78)	<0.001†
Chronic pulmonary disease	0.56 (0.49–0.64)	<0.001†
Liver disease	0.51 (0.37–0.71)	<0.001†
Solid cancer	0.59 (0.39–0.89)	0.013†
Peripheral vessel disease	1.19 (1.01–1.41)	0.035†
Prior myocardial infarction	0.63 (0.52–0.77)	<0.001†
Prior PCI	0.50 (0.27–0.92)	0.026†
Prior CABG	0.17 (0.13–0.23)	<0.001†

The following variables have been included in the Logistic regression models: age, sex, primary expected payer, median household income, residency in same state as admission hospital, hospital bed size, hospital teaching status, length of stay, diabetes, hypertension, anemia, chronic lung disease, arrhythmias, chronic liver disease, solid cancer, peripheral vascular disease, renal failure, prior PCI, prior CABG, prior myocardial infarction. aOR indicates adjusted odds ratio; AS, aortic stenosis; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; and SAVR, surgical aortic valve replacement.

*Reference groups are "small hospital bed size" (hospital bed size category), "Medicare" (primary expected payer category), "lowest quartile" (median household income category), and "nonteaching hospitals" (hospital teaching status category).

†$P<0.05$.

magnetic resonance, not only for calcium quantification but also to better define flow status, left ventricular adaptive remodeling, and fibrosis distribution.[39] Finally, symptomatic moderate AS, irrespective of sex, is associated with impaired survival and increased heart failure hospitalizations, probably evidencing the initial uncoupling between left ventricular contractile capacity and the valvuloarterial impedance and demarking a potentially higher risk of accelerated progression to severe stenosis.[40,41] In the meta-analysis of Franke et al.[42] intervention on moderate AS with AVR, either surgical or percutaneous, showed a significant mortality reduction (45% decreased risk of all-cause mortality). However, more data from the ongoing randomized trials investigating the potential benefit of early intervention in moderate AS, namely PROGRESS TAVR (A Prospective, Randomized, Controlled Trial to Assess the Management of Moderate Aortic Stenosis

Table 7. Conditional Logistic Multivariable Model with Adjusted Odds Ratio and 95% CI for Transcatheter Aortic Valve Implantation, in Readmitted Patients With Severe AS Features, After 1:1 matching

Variables	TAVI	
	aOR (95% CI)	*P* value
Female sex	0.79 (0.75–0.84)	<0.001†
Age	1.01 (1.00–1.01)	<0.001†
Hospital bed size*	…	…
Medium	1.27 (1.16–1.39)	<0.001†
Large	1.64 (1.51–1.79)	<0.001†
Length of stay	1.02 (1.01–1.03)	<0.001†
Primary expected payer*	…	…
Medicaid	0.37 (0.29–0.49)	<0.001†
Private insurance	0.67 (0.58–0.77)	<0.001†
Resident in same hospital state	0.73 (0.63–0.84)	<0.001†
Median household income (highest quartile)*	1.31 (1.20–1.44)	<0.001†
Hospital teaching status*	1.28 (1.19–1.37)	<0.001†
Diabetes	1.04 (0.96–1.13)	0.317
Hypertension	1.04 (0.93–1.16)	0.471
Anemia	0.94 (0.85–1.05)	0.253
Renal failure	0.72 (0.68–0.77)	<0.001†
Arrhythmias	0.79 (0.74–0.84)	<0.001†
Chronic pulmonary disease	0.79 (0.74–0.84)	<0.001†
Liver disease	0.78 (0.65–0.94)	0.009†
Solid cancer	0.75 (0.62–0.90)	0.002†
Peripheral vessel disease	1.13 (1.04–1.23)	0.004†
Prior myocardial infarction	0.85 (0.78–0.93)	<0.001†
Prior PCI	1.13 (0.90–1.42)	0.291
Prior CABG	1.06 (0.97–1.15)	0.183

The following variables have been included in the Logistic regression models: age, sex, primary expected payer, median household income, residency in same state as admission hospital, hospital bed size, hospital teaching status, length of stay, diabetes, hypertension, anemia, chronic lung disease, arrhythmias, chronic liver disease, solid cancer, peripheral vascular disease, renal failure, prior PCI, prior CABG, prior myocardial infarction. aOR indicates adjusted odds ratio; AS, aortic stenosis; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; and TAVI, transcatheter aortic valve implantation.

*Reference groups are "small hospital bed size" (hospital bed size category), "Medicare" (primary expected payer category), "lowest quartile" (median household income category), and "nonteaching hospitals": (hospital teaching status category).

†$P<0.05$.

by Clinical Surveillance or Transcatheter Aortic Valve Replacement; ClinicalTrials.gov: NCT04889872) and Evolut EXPAND TAVR II Pivotal Trial (ClinicalTrials.gov: NCT05149755), are warranted.

Second, interpreting symptoms or the lack thereof is notoriously difficult, particularly in older deconditioned and sedentary patients. This could be even more pronounced in the female population where not only noncardiac comorbidities are more prevalent but also self-evaluation of their own cardiac disease and its impact on their daily functioning is less severe compared with men.[43–45] Behavioral models suggest that patients' perceptions of the severity of their disease play an important role in determining the patients' engagement in behaviors related to the disease. Thus, in female patients with severe AS, the clinician should probably be careful in the assessment of typical and especially atypical, often underestimated by the patient, symptoms that could lead to a late referral to intervention in case of clinical misjudgment with a tremendous impact on prognosis.

Third, a potential difference in referral to AS intervention is most probably not only secondary to clinical differences among sexes but also from potential access barriers that may stem from various sources, including sex biases in patient selection criteria, referral patterns, and disparities in patient–physician communication. Patient–provider sex concordance has been shown to potentially influence the perception of symptoms and consequently outcomes: Greenwood et al. have shown that the in-hospital survival rates of female patients with acute myocardial infarction treated by male doctors were worse, but this gap was no more evident when women were treated by women clinicians.[46] Furthermore, in a previous large US study investigating 1 583 028 Medicare hospitalizations with a primary medical admission condition, women physicians were more likely to follow guideline- and evidence-based care, with lower 30-day mortality and readmission rates.[47] Currently, female proceduralists are still underrepresented in both the interventional and surgical fields and rarely are women patients with valvular heart disease treated by women.[48,49]

Finally, yet importantly, socioeconomic factors may play a pivotal role in perpetuating sex disparities in access to AS intervention: it is acknowledged that differences in access to socioeconomic resources are crucial determinants of the so-called "social gradient of health," the inverse associations between socioeconomic position and increased mortality and morbidity.[50] This can be particularly true in a predominantly private health system such as the United States, where disparities in health care access and insurance coverage can significantly affect the ability of individuals, particularly women, to seek timely diagnosis and treatment[51] and where the high costs associated with aortic valve interventions may pose a substantial financial barrier, disproportionately affecting individuals of lower socioeconomic status.[52]

The results of our study should then prompt a couple of questions. Firsy, on a national level, how systematic and comprehensive is the diagnostic approach to AS? Second, can the implementation of sex-specific hemodynamic indexes improve the prognosis of female patients with symptomatic severe AS

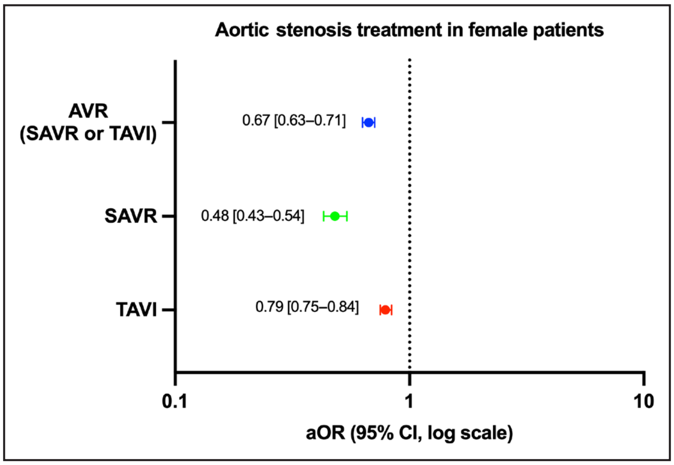

Figure 3. Adjusted odds ratio and relative 95% CI for AVR, SAVR and TAVI of female patients with AS with severe features.
Reference group are male patients. aOR indicates adjusted odds ratio; AS, aortic stenosis; AVR, aortic valve replacement; SAVR, surgical aortic valve replacement; and TAVI, transcatheter aortic valve implantation.

and simplify the workup process also in nonacademic centers? By trying to answer these questions and further understand the underlying factors contributing to these disparities, we can work toward reducing sex-related barriers, promoting equitable access to these life-saving procedures, and improving outcomes for all individuals with AS.

We acknowledge the several limitations of this study. First, selection bias due to inaccuracies in coding and missing data cannot be completely excluded and some data that could have influenced outcomes, such as ethnicity, are inherently not available in the NRD. The database itself does not allow direct capture of the severity of AS and, thus, we cannot exclude that a small proportion of patients with symptomatic severe AS who received AVR at 90-day readmission period have not been intercepted. Moreover, due to the absence of patient-level hemodynamic data, we cannot exclude that a quota of patients with symptomatic AS and severe features had only hemodynamic moderate AS. Patients with asymptomatic severe AS were not captured by this analysis. However, in this scenario indication and timing for treatment are still controversial and lack of homogeneity across centers and operators is presumable. In the NRD, each year is independent and follow-up of patients across years is not possible. Hence, we focused our analysis on 90-day readmission period to find the balance between enough time for AVR to occur and not losing sample size with obligatory data removal with longer follow-up. However, we do not expect a significant variation of the female-to-male ratio of indication to AVR at longer follow-up. Furthermore, due to the inherent administrative nature of the NRD, only data about in-hospital all-cause mortality are collected. Thus, distinguishing between cardiovascular and noncardiovascular causes of death and retrieving information about out-of-hospital mortality were not possible. However, we have performed the nested case–control analysis with a 1:1 matching ratio to tackle potential competing risk and selection bias in our cohort as much as possible. Finally, the retrospective nature of the study cannot fully exclude unknown residual confounding bias and allows only evaluations of associations that are hypothesis generating. Nevertheless, the large sample size should allow sufficiently powered analyses to detect sex differences in selection for AVR.

CONCLUSIONS

In conclusion, this large national retrospective study reveals that female patients with AS and severe features have significantly lower use of AVR, either SAVR or TAVI, at 90-day readmission period, independently from comorbidities, clinical presentation, and hospital-related factors. Future studies are needed to detect the underlying mechanisms and global initiatives are warranted to diminish the observed disparities.

ARTICLE INFORMATION

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Supplemental Material

Data S1. STROBE checklist
Tables S1–S2
Figures S1–S3

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