European Heart Journal - Valvular and Structural Heart Disease (2026) **2**, xwag009
https://doi.org/10.1093/ehjvshd/xwag009

ORIGINAL ARTICLE
Aortic valvular heart disease

Challenges in the timely management of severe aortic stenosis: a multicentre analysis of delayed transcatheter aortic valve implantation referrals and gender disparities

Angelicarosa Cascone[1], Francesco Federico[2], Giulia Ghizzoni[2], Ciro Vella[2], Barbara Bellini[2], Giulia Botti[1,2], Marco Ancona[2], Luca Ferri[2], Filippo Russo[2], Thomas Lescure[3], Ana Laffond[4], Nicole Karam[3,5], Ignacio Cruz-Gonzalez[4], Matteo Montorfano [1,2], and Alaide Chieffo [1,2,*]

[1]Vita-Salute San Raffaele University, Via Olgettina 58, Milan 20132, Italy; [2]IRCCS San Raffaele Scientific Institute, Interventional Cardiology Unit, Via Olgettina 60, Milan 20132, Italy; [3]Cardiology Department, European Hospital Georges Pompidou, Paris, France; [4]University Hospital of Salamanca, CIBER-CV, IBSAL, Salamanca, Spain; and [5]Clemenceau Medical Center, Balamand University, Beirut, Lebanon

Received 7 January 2026; revised 27 January 2026; accepted after revision 2 February 2026; online publish-ahead-of-print 20 February 2026

Abstract

Background Gender-related disparities in diagnosis and referral to transcatheter aortic valve implantation (TAVI) remain incompletely understood.

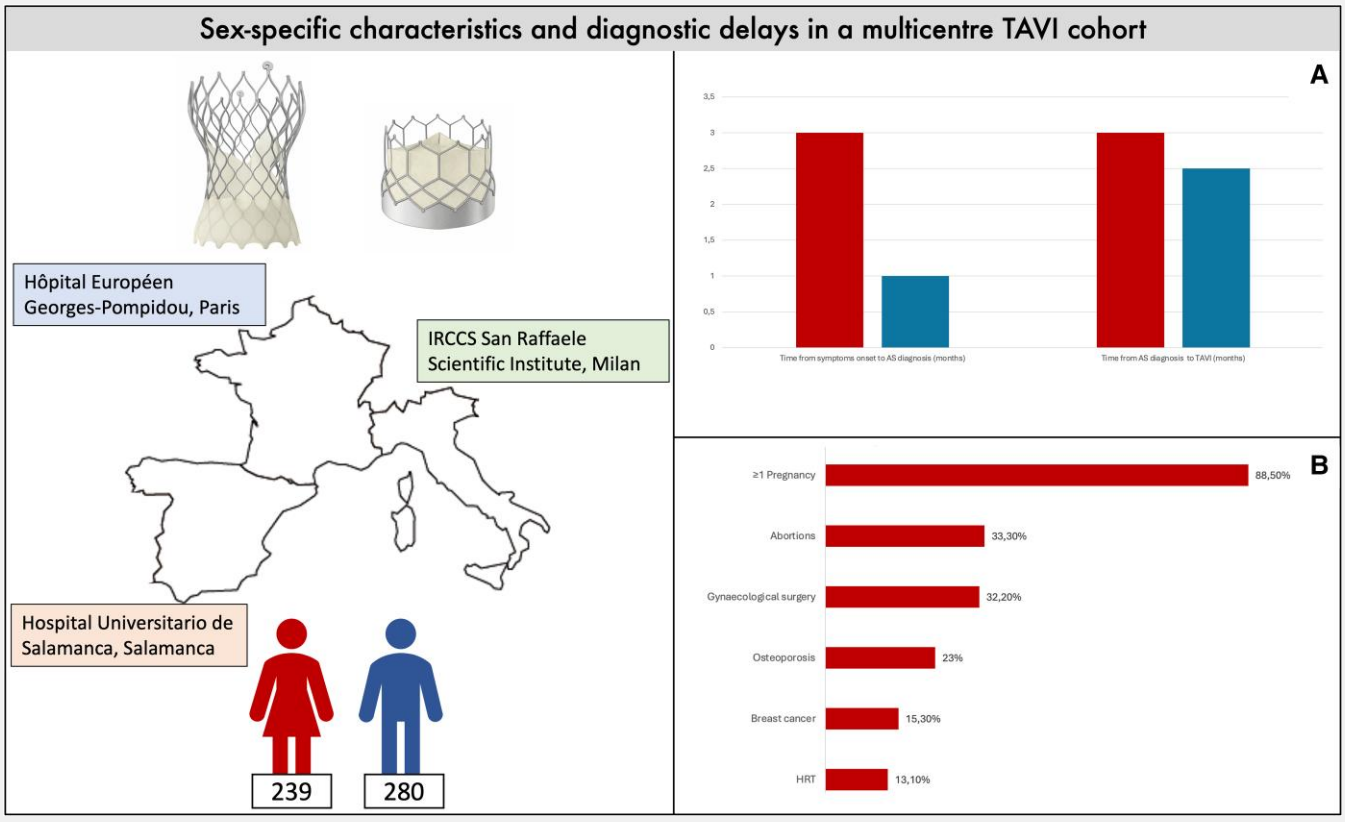
Aims This study aims to assess sex-related differences in diagnostic and therapeutic delays to TAVI and to explore sex-related disparities in management and clinical characteristics of patients with severe aortic stenosis (AS).

Methods and results This multicentre, observational study included 519 patients (46.1% women) with severe symptomatic AS referred for TAVI in 2023 across three European centres. Outcomes were assessed according to VARC-3. Female-specific clinical history was systematically collected. Women were older, with higher surgical risk (STS Score: 4.5 [3.0–6.6] vs. 2.8 [1.7–4.0], $P < .001$) and more advanced symptoms (New York Heart Association functional Classes III and IV 87 vs. 77, $P = .014$). Aortic annulus dimensions and valve area were smaller in women (both $P < .001$). Women experienced longer delays from symptom onset to diagnosis (3 [0–9] vs. 1 [0–4] month, $P < .001$), with notable inter-centre variability. However, time from diagnosis to TAVI was similar (3 [1–5] vs. 2.5 [1–4.5] months, $P = .220$). In-hospital mortality (2.5% vs. 1.8%, $P = .555$), bleeding, major vascular complications, and conduction disturbances did not differ by sex. At 6 months, functional status improved significantly; mortality (4.1% vs. 5.3%, $P = .685$), rehospitalization, and device success (84.6% vs. 85.8%, $P = .252$) were comparable between sexes. Female-specific characteristics, including pregnancy, gynaecological history, and hormone therapy, were not significantly associated with clinical outcomes.

Conclusions Women faced longer diagnostic delays, indicating persistent sex-based disparities in the timely recognition of severe AS. Nevertheless, clinical outcomes after TAVI were similar between sexes, supporting comparable treatment effectiveness.

* Corresponding author. Email: chieffo.alaide@hsr.it

Graphical Abstract



Sex-specific characteristics and diagnostic delays in a multicentre TAVI cohort. Sex-specific differences in a multicentre cohort of patients undergoing TAVI in 2023. (A) Time from symptom onset to aortic stenosis diagnosis and from diagnosis to TAVI, stratified by sex. (B) Prevalence of female sex-specific clinical characteristics. Abbreviations: AS, aortic stenosis; TAVI, transcatheter aortic valve implantation; HRT, hormone replacement therapy.

Keywords Aortic stenosis • Transcatheter aortic valve implantation • Gender disparities • Diagnostic delay • Treatment delay

Introduction

Degenerative aortic valve disease is the most common cause of valvular heart disease in the Western world, leading to significant morbidity and mortality.[1,2] Both European and American guidelines assign a Class I-a recommendation for intervention in adults with severe aortic stenosis (AS) and symptoms of dyspnoea, heart failure, angina, and syncope.[3,4] While the prevalence of AS between men and women is similar across epidemiological studies, sex differences have been detected in terms of pathophysiological progression, clinical presentation, and prognosis.[5] Historically, women were less likely to receive aortic valve replacement (AVR), though recent increases in the use of transcatheter aortic valve implantation (TAVI) among women, who now represent approximately half of the patients undergoing TAVI,[6] have been observed.[7] However, there is still a limited understanding of the factors contributing to sex-based disparities in the diagnosis and treatment of AS. Delays in diagnosis and referral have been associated with worse clinical outcomes,[8] and observational studies suggest that women tend to be diagnosed later, presenting with a higher burden of frailty and lower survival rates.[9,10] Large-scale studies focusing specifically on women have begun to address this gap. Women's International (WIN) TAVI registry was the first all-women multinational, prospective registry evaluating women with severe AS undergoing TAVI. Enrolling more than 1000 intermediate-to-high risk women, the registry provided valuable insights into female-specific anatomical and procedural characteristics as well as predictors of outcomes.[11,12] It demonstrated that at 30 days, the Valve Academic Research Consortium (VARC)-2 early safety composite endpoint occurred in 14.0% of patients, with low all-cause mortality (3.4%) and stroke rates (1.3%). Independent predictors of early safety and efficacy endpoints included age, prior stroke, left ventricular ejection fraction, device generation, and obstetric history. Recently, the randomized research in all-comers women with AS (RHEIA) trial was the first all-female population randomized clinical trial comparing TAVI vs. surgical AVR, demonstrating that, at 1 year, TAVI was associated with a lower incidence of the primary composite endpoint of death, stroke, or rehospitalization.[13] These studies highlight the necessity of sex-specific research in structural heart disease to optimize the management of women undergoing TAVI. Concerning surgical AVR, several studies have shown that, although women referred for surgery tend to be older and more symptomatic than men, operative and long-term mortality are not increased.[14,15] However, despite growing evidence on sex-related differences in outcomes and procedural characteristics, it remains unclear whether potential diagnostic and therapeutic delays influence clinical outcomes, highlighting the need for future investigation.

The aim of our study was to evaluate potential sex related delays in the diagnosis of AS and referral to TAVI. Additionally, potential sex-related disparities in AS management and sex-specific characteristics that could influence outcomes were investigated.

Methods

This multicentre, observational study included consecutive patients with severe symptomatic AS referred for TAVI in 2023 to three European centres: IRCCS San Raffaele Scientific Institute, Milan, Italy (Milan; $n = 234$), Hôpital Européen Georges-Pompidou, Paris, France (Paris; $n = 135$), and Hospital Universitario de Salamanca, Salamanca, Spain (Salamanca; $n = 150$).

All participating centres were designated Heart Valve Centres, characterized by multidisciplinary heart teams, in line with current 2025 ESC/EACTS guidelines for the management of valvular heart disease.[4] Patient eligibility for TAVI was determined according to the current ESC guidelines.[4] The heart team ensured guideline-directed patient evaluation, shared decision-making based on clinical evidence and patient preferences and optimal selection of treatment strategies, in accordance with guideline recommendations.

Severe AS was defined according to current guideline recommendations, based on a comprehensive clinical and echocardiographic assessment, including aortic valve area (AVA), peak aortic jet velocity, and transaortic mean gradients. Severe AS was primarily identified by an AVA $\leq$ 1 cm^2 or indexed AVA $\leq$ .6 cm^2/m^2. Accordingly, gradient severity was assessed, including both high-flow, high-gradient (HF-HG) and low-gradient severe AS. Low-gradient AS encompassed classical low-flow, low-gradient (LF-LG) with reduced left ventricular ejection fraction (LVEF), normal-flow, low-gradient (NF-LG), and the paradoxical LF-LG with preserved LVEF. In particular, the latter phenotype, comprising a high proportion of women, older patients with restrictive LV physiology, is associated with a higher surgical risk compared with high-gradient AS.[16]

Patient evaluation and procedural planning

Pre-screening included a detailed assessment of medical history and standard care diagnostic imaging. Imaging evaluation comprised transthoracic and/or transoesophageal echocardiography and multidetector computed tomography, with measurements performed according to current guidelines.[4] Procedural decisions, including access route, device selection, use of aortic valve pre- and post-dilation, and adjunctive interventional strategies, were determined by the multidisciplinary heart team, based on clinical, anatomical, and imaging findings.

Female-specific data collection

Female-specific data, including history of pregnancy, abortions, pregnancy complications (such as gestational hypertension, gestational diabetes, ectopic pregnancy, HELLP syndrome), breastfeeding, breast or gynaecological cancer, gynaecological surgery, menstrual history, use of hormone replacement therapy, and osteoporosis, were collected through structured patient interviews and review of medical records.

Follow-up

Follow-up included phone contact or clinic visits at 6 months to assess clinical status and adverse events, as defined by the VARC-3.[17]

Study endpoints and definitions

The primary aim of this study was to evaluate sex-related delays in diagnosis and treatment of AS, defined as:

- *Diagnostic delay*: time, measured in months, from patient-reported symptom onset to echocardiographic confirmation of severe AS.
- *Therapeutic delay*: time, in months, from diagnosis to index TAVI procedure.

Both time intervals were retrieved from clinical documentation or, if unavailable, self-reported by the patient.

Sex-related differences in the management of severe symptomatic AS were analysed, along with an exploration of female-specific clinical characteristics associated with disease presentation.

Secondary endpoints included the assessment of clinical outcomes according to the Valve Academic Research Consortium (VARC)-3 criteria[17]:

- *Technical success* of the TAVI procedure, defined as freedom from procedural mortality, successful vascular access, delivery, and retrieval of the transcatheter valve system, correct positioning of a single prosthetic valve in the appropriate anatomical location and absence of the need for surgery or intervention related to the device or major vascular, access-related, or cardiac structural complications.
- *Device success at 6 months*, defined as meeting the criteria for technical success, freedom from mortality, reintervention, device-related complications or major vascular, access-related or cardiac structural complications, and intended valve performance, characterized by a mean gradient < 20 mmHg, peak velocity < 3 m/s, Doppler velocity index $\geq$ .25, and less than moderate aortic regurgitation.
- *Mid-term safety at 6 months*, including freedom from all-cause mortality, stroke, VARC type 2–4 bleeding, major vascular, access-related or cardiac structural complications, stage 3–4 acute kidney injury, moderate or severe aortic regurgitation, new permanent pacemaker implantation due to procedure-related conduction disturbances, and need for surgery or intervention related to the device.
- *Mid-term clinical outcomes at 6 months*, including freedom from all-cause mortality, hospitalization, myocardial infarction, bioprosthetic valve dysfunction or failure, and major adverse cardiac events.

Statistical analysis

Descriptive statistic was used to describe the characteristics of the study population. Continuous variables were reported as mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate, and compared using Student's *t*-test or the Mann–Whitney *U* test. Categorical variables were expressed as absolute frequencies and percentages and compared with chi-square or Fisher's exact test. Correlations between AS and sex (female)-specific data were assessed by univariate and multivariate logistic regression analyses. Time-to-event analyses were performed using Kaplan–Meier estimates, with comparisons stratified by sex. All analyses were conducted using RStudio (v4.4.1), and a two-sided *P*-value < .05 was considered indicative of statistical significance.

Results

Study population and clinical presentation

Among the 519 patients, 239 (46.1%) were women. Women were older (median age: 83 [80–87] vs. 81.5 [77–86] years, $P < .001$) but had similar body mass index to men (median BMI [kg/m^2]: 25.7 [22.9–29.8] vs. 25.9 [23.4–28.4], $P = .840$). Regarding traditional cardiovascular risk factors, women were less likely to be current (3 (1.3%) vs. 16 (5.7%), $P < .001$) and former smokers (26 (11.0%) vs. 102 (36.6%), $P < .001$), while no significant differences were observed for diabetes mellitus (64 (26.9%) vs. 92 (33.0%), $P = .133$), arterial hypertension (190 (79.5%) vs. 215 (77.1%), $P = .503$), dyslipidaemia (140 (58.8%) vs. 173 (62.0%), $P = .460$), family history of coronary artery disease (20 (8.4%) vs. 22 (7.9%), $P = .819$), and severe chronic kidney disease (32 (13.8%) vs. 33 (11.9%), $P = .573$). Coronary artery disease was less prevalent among women (66 (27.6%) vs. 130 (46.6%), $P < .001$) as well as peripheral vascular disease (26 (11%) vs. 50 (18%), $P = .034$).

However, women had higher surgical risk (median STS Score: 4.5 [3.0–6.6] vs. 2.8 [1.7–4.0], $P < .001$, median Euroscore II: 2.6 [2.0–3.9] vs. 2.3 [1.5–3.6], $P = .003$), smaller aortic annuli (mean diameter [mm]: 23.1 ± 1.8 vs. 26.1 ± 2.1, $P < .001$; median perimeter [mm]: 73.0 [70.0–76.2] vs. 82.6 [77.6–86.7], $P < .001$; median area [mm^2]: 419 [384.8–458.3] vs. 539 [484.5–607.5], $P < .001$). Moreover, women presented with a smaller aortic valve area (.67 [.54–.81] vs. .76 [.62–.90], $P < .001$). Notably, the prevalence of bicuspid aortic valve was twice as common in men (12 vs. 23, $P = .201$).

No significant differences were observed for the type of symptoms between sexes. Conversely, a higher proportion of women presented with more severe New York Heart Association (NYHA) functional class (NYHA Classes III and IV 87 vs. 77, $P = .014$).

Among female sex-specific characteristics, 88.5% had at least one pregnancy, with a median of three pregnancies. The history of abortion was reported by 61 (33.3%) women, while pregnancy-related complications were noted in 10 patients (5.5%). The median age of menopause was 52 years; 59 (32.2%) women had undergone previous gynaecological surgery, 28 (15.3%) had a history of breast cancer, 9 (4.9%) had a history of gynaecological cancer, and 42 (23%) were diagnosed with osteoporosis. Additionally, 24 women (13.1%) had received hormonal replacement therapy. Baseline clinical and procedural characteristics are summarized in *Table 1*.

The time intervals from symptom onset to diagnosis and from diagnosis to TAVI were analysed and stratified by sex and hospital. The analysis revealed notable inter-centre variability as well as sex-related differences. Overall, women experienced longer diagnostic delays than men, with a median time of 3 [0–9] versus 1 [0–4] month ($P < .001$), When stratified by hospital, the median diagnostic delay

Table 1 Baseline demographics, clinical, and procedural characteristics

Variable	Overall ($n = 519$)	Women ($n = 239$)	Men ($n = 280$)	*P*-value
Age (years), median (IQR)	82 (78–86)	83 (80–87)	81.5 (77–86)	**<.001**
BMI (kg/m^2), median (IQR)	25.8 (23.2–29.1)	25.7 (22.9–29.8)	25.9 (23.4–28.4)	.840
Family history of CAD, *n* (%)	42 (8.1)	20 (8.4)	22 (7.9)	.819
Smoker, *n* (%)	21 (4.1)	3 (1.3)	16 (5.7)	**<.001**
Previous smoker, *n* (%)	126 (24.4)	26 (11.0)	102 (36.6)	**< .001**
Hypertension, *n* (%)	405 (78.2)	190 (79.5)	215 (77.1)	.503
Dyslipidemia, *n* (%)	313 (60.5)	140 (58.8)	173 (62.0)	.460
Diabetes mellitus, *n* (%)	156 (30.2)	64 (26.9)	92 (33.0)	.133
PVD, *n* (%)	76 (14.7)	26 (11)	50 (18)	**.034**
eGFR				.573
>30 and ≤ 60, *n* (%)	214 (41.9)	92 (39.5)	122 (43.9)	
≤30, *n* (%)	65 (12.7)	32 (13.8)	33 (11.9)	
COPD, *n* (%)	53 (10.3)	17 (7.1)	36 (12.9)	**.044**
CAD, *n* (%)	196 (37.8)	66 (27.6)	130 (46.6)	**<.001**
Prior PCI, *n* (%)	130 (25.1)	44 (18.5)	86 (30.7)	**.002**
Prior cardiac surgery, *n* (%)	46 (8.9)	14 (5.9)	32 (11.4)	**.038**
Prior TAVI, *n* (%)	4 (.8)	2 (.8)	2 (.7)	1
Prior stroke or TIA, *n* (%)	51 (9.8)	19 (7.9)	32 (11.5)	.233
Prior AF, *n* (%)	166 (32.0)	83 (34.7)	83 (29.7)	.264
Prior PM, *n* (%)	41 (7.9)	17 (7.1)	24 (8.6)	.652
Anaemia, *n* (%)	234 (46.2)	102 (44.3)	132 (47.7)	.513
STS Score, median (IQR)	3.4 (1.7–3.8)	4.5 (3.0–6.6)	2.8 (1.7–4.0)	**<.001**
EuroSCORE II, median (IQR)	2.4 (2.4–3.8)	2.6 (2.0–3.9)	2.3 (1.5–3.6)	**.003**
NYHA				
I, *n* (%)	80 (16.0)	27 (11.8)	53 (19.5)	**.026**
II, *n* (%)	257 (51.3)	115 (50.2)	142 (52.2)	.723
III, *n* (%)	144 (28.7)	79 (34.5)	65 (23.9)	**.012**
IV, *n* (%)	20 (4.0)	8 (3.5)	12 (4.4)	.769
Angina, *n* (%)	92 (17.9)	40 (16.7)	52 (18.8)	.657
Syncope, *n* (%)	50 (9.7)	24 (10.1)	26 (9.4)	.883
Time from symptoms onset to AS diagnosis (months), median (IQR)	1 (0–6)	3 (0–9)	1 (0–4)	**<.001**
Time from AS diagnosis to TAVI (months), median (IQR)	3 (1–5)	3 (1–5)	2.5 (1–4.5)	.220
LVEF (%), median (IQR)	60 (55–65)	60 (57–65)	60 (50–64)	**< .001**
Mean AV gradient (mmHg), median (IQR)	43 (38–51)	44 (39–52)	42 (38–50)	**.044**

Continued

Table 1 ***Continued***

Variable	Overall ($n = 519$)	Women ($n = 239$)	Men ($n = 280$)	*P*-value
Aortic regurgitation				.878
None, *n* (%)	158 (34.1)	70 (32.9)	88 (35.2)	
Mild, *n* (%)	232 (50.1)	110 (51.6)	122 (48.8)	
Moderate, *n* (%)	60 (12.3)	28 (13.1)	32 (12.8)	
Severe, *n* (%)	13 (2.8)	5 (2.3)	8 (3.2)	
Aortic valve area (cm^2), median (IQR)	.7 (.6–.86)	.67 (.54–.81)	.76 (.62–.90)	**<.001**
Anulus mean diameter (mm), mean ± SD	24.3 ± 2.5	23.1 ± 1.8	26.1 ± 2.1	**<.001**
Anulus perimeter (mm), median (IQR)	76.8 (72.7–83.1)	73 (70.0–76.2)	82.6 (77.6–86.7)	**<.001**
Anulus area (mm^2), median (IQR)	477 (419.0–545.0)	419 (384.8–458.3)	539.0 (484.5–607.5)	**<.001**
Bicuspid AV, *n* (%)	35 (6.8)	12 (5.0)	23 (8.27)	.201
Femoral access, *n* (%)	496 (95.6)	229 (95.8)	267 (95.4)	.201
Concomitant PCI, *n* (%)	33 (6.4)	8 (3.3)	25 (8.9)	**.016**
Femoral PTA with stent, *n* (%)	30 (5.8)	16 (6.7)	14 (5.0)	.517
Implantation of multiple bioprosthesis, *n* (%)	4 (.8)	3 (1.3)	1 (.4)	.502
Valve malposition, *n* (%)	6 (1.2)	4 (1.7)	2 (.7)	.536
Final mean gradient < 20 mmHg, *n* (%)	380 (73.2)	177 (74.1)	203 (72.5)	1
Final aortic regurgitation ≥ moderate, *n* (%)	4 (.8)	2 (.8)	2 (.7)	.948
Devices				
CoreValve Evolut, *n* (%)	270 (52.0)	117 (49.0)	153 (54.6)	**.028**
Edwards Sapien, *n* (%)	126 (24.3)	47 (19.7)	79 (28.2)	**.004**
Acurate Neo 2, *n* (%)	66 (12.7)	34 (14.2)	32 (11.4)	.805
Myval and Hydra, *n* (%)	11 (2.1)	6 (2.6)	5 (1.8)	.763
Navitor, *n* (%)	15 (2.9)	9 (3.8)	6 (2.1)	.438
Allegra, *n* (%)	28 (5.4)	23 (9.6)	5 (1.8)	**<.001**

AF, atrial fibrillation; AS, aortic stenosis; AV, aortic valve; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF left ventricle ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PCI, percutaneous coronary intervention; PM, pacemaker; PVD, peripheral vascular disease; PTA, percutaneous transluminal angioplasty; STS, Society of Thoracic Surgeons' Score; TAVI, transcatheter aortic valve implantation; TIA, transient ischemic attack.

Table 2 Diagnostic and therapeutic delay stratified by sex and hospital

Delay type	Hospital	Women (months)	Men (months)	*P*-value
Diagnostic delay	Milan	1 (0–5.5)	1 (0–4)	.301
	Paris	6 (2–8)	3 (1–7)	.201
	Salamanca	6 (1–12)	1 (0–3)	<.001
Therapeutic delay	Milan	2 (1–4.5)	2 (1–4)	.095
	Paris	5 (2–9)	7 (3.5–12.5)	.367
	Salamanca	3 (1–6)	3 (1–4.7)	.355

for women was 1 [0–5.5] month in Milan ($n = 126$, 53.8%), 6 [2–8] months in Paris ($n = 76$, 56.3%), and 6 [1–12] months in Salamanca ($n = 72$, 52.0%). Men experienced diagnostic delays of 1 [0–4] month in Milan, 3 [1–7] months in Paris, and 1 [0–3] month in Salamanca. Differences between women and men within each centre were statistically significant only in Salamanca ($P < .001$), while no significant sex differences were observed in Milan ($P = .301$) or Paris ($P = .201$). Paris showed significantly longer diagnostic delays compared to Milan and Salamanca ($P < .05$), regardless of sex. Therapeutic delay was similar between women and men overall (3 [1–5] versus 2.5 [1–4.5] months, $P = .220$). Diagnostic and therapeutic delay stratified by sex and hospital are reported in *Table 2* and *Figs 1* and *2*.

In-hospital outcomes

Eleven patients (2.1%) died during hospitalization, all from cardiovascular causes, with no significant sex differences (6 (2.5%) women vs. 5 (1.8%) men, $P = .555$). Technical success was achieved in 510 patients (98.3%). Myocardial infarction occurred in 5 patients (0 (0%) vs. 5 (1.8%), $P = .07$). Bleeding requiring transfusion was reported in 65 cases (12.5%) and 20 (3.8%) major vascular complications occurred, with no significant differences between sexes. Of note, no significant sex-based differences were recorded in the rates of new onset or worsened conduction

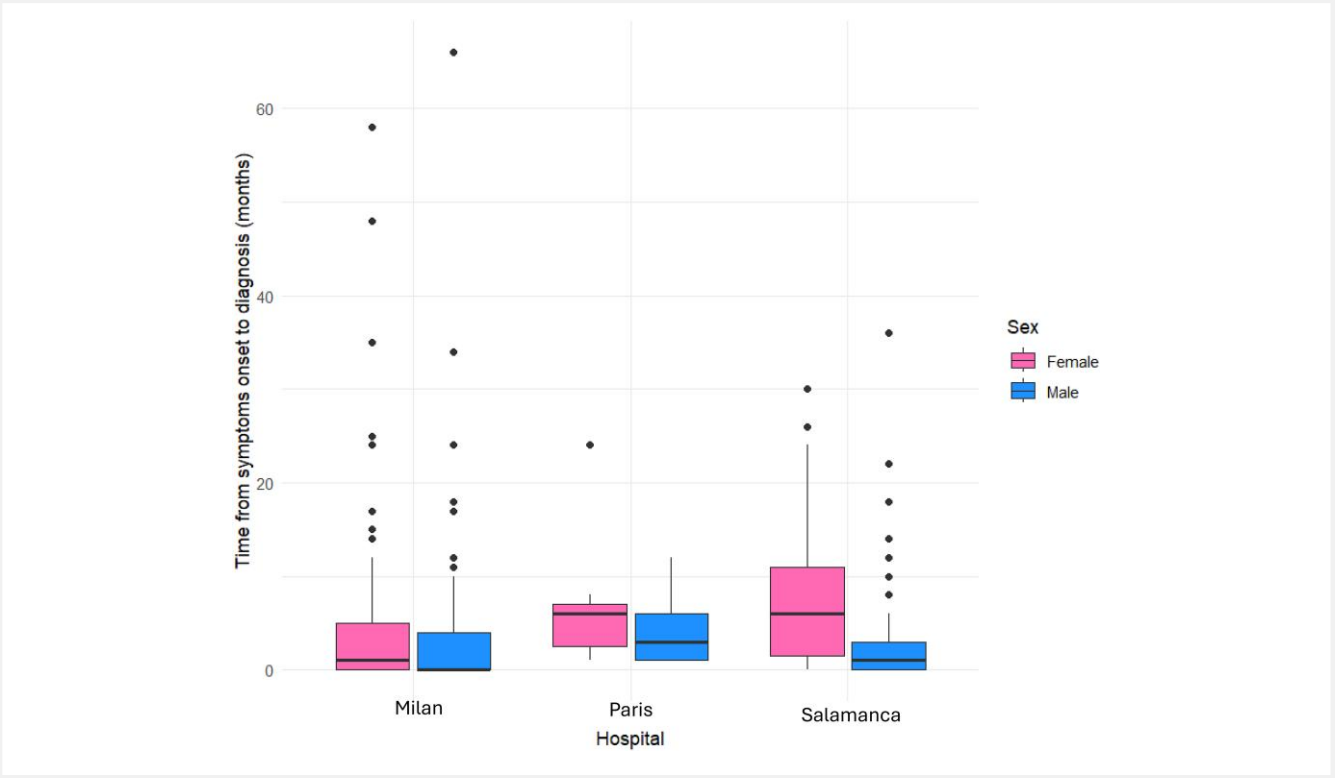


Figure 1 Boxplot illustrating the distribution of diagnostic delays stratified by sex and hospital site

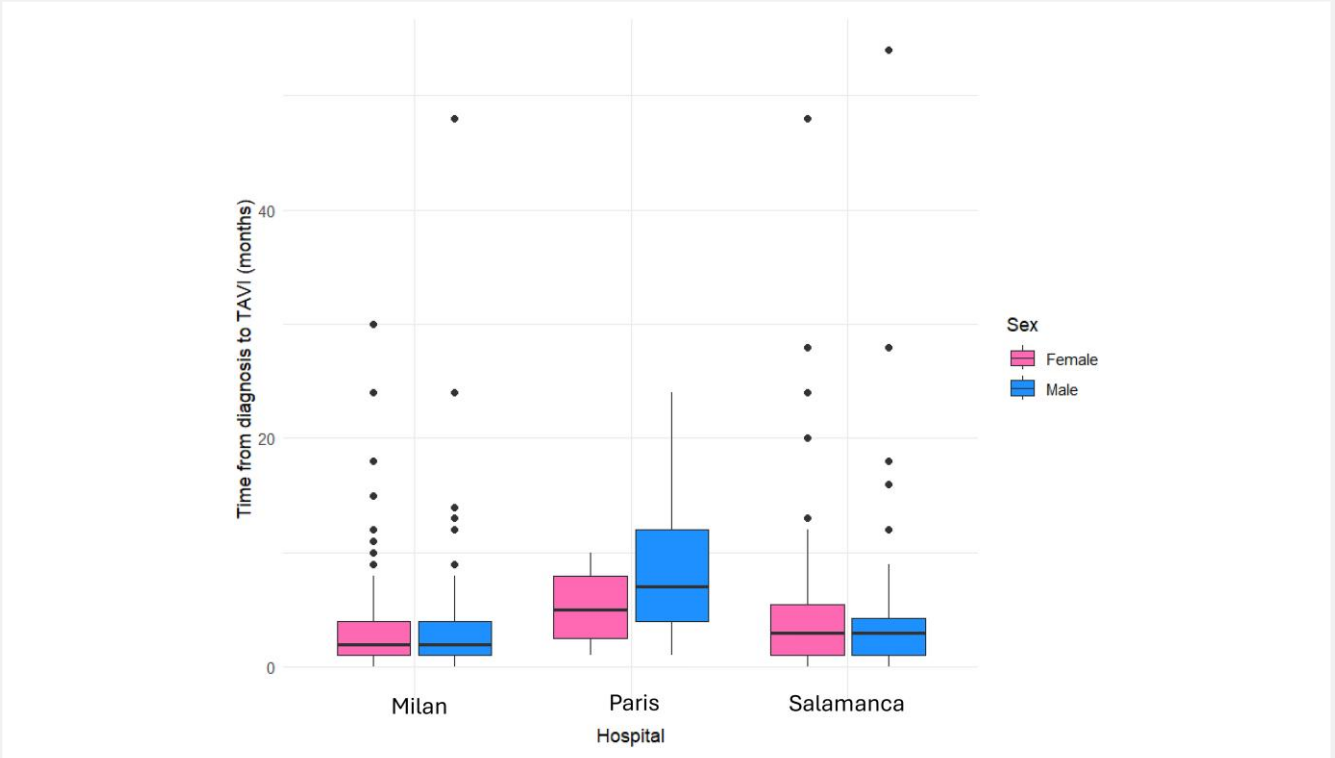


Figure 2 Boxplot illustrating the distribution of therapeutic delays stratified by sex and hospital site

Table 3 In-hospital clinical outcomes

Variable	Overall ($n = 519$)	Women ($n = 239$)	Men ($n = 280$)	OR (95% CI)	*P*-value
All-cause death, *n* (%)	11 (2.2)	6 (2.5)	5 (1.8)	.680 (.21–2.26)	.555
Cardiovascular death, *n* (%)	10 (1.9)	5 (2.1)	5 (1.8)	.895 (.25–3.23)	1
Non-cardiovascular death, *n* (%)	1 (.2)	0 (0)	1 (.4)	.526 (.45–.61)	1
Technical success, *n* (%)	510 (98.3)	233 (97.5)	277 (98.9)	2.972 (.57–15.46)	.175
Myocardial infarction, *n* (%)	5 (1.0)	0 (0)	5 (1.8)	.545 (.50–.59)	**.07**
Acute kidney injury				1.578	.127
Type 1, *n* (%)	45 (9.1)	14 (6.3)	31 (11.4)	(.88–2.84)	
Type 2, *n* (%)	6 (1.2)	3 (1.4)	3 (1.1)		
Type 3, *n* (%)	2 (.4)	2 (.9)	0 (0)		
Type 4, *n* (%)	1 (.2)	0 (0)	1 (.4)		
Vascular and access-related complication				.686 (.37–1.29)	.237
Minor, *n* (%)	23 (4.7)	12 (5.4)	11 (4.1)		
Major, *n* (%)	20 (3.8)	11 (5.0)	9 (3.2)		
Bleeding				.764	.311
Type 1, *n* (%)	25 (5.1)	13 (5.9)	12 (4.4)	(.45–1.29)	
Type 2, *n* (%)	37 (7.5)	17 (7.7)	20 (7.4)		
Type 3, *n* (%)	1 (.2)	1 (.5)	0 (0)		
Type 4, *n* (%)	2 (.4)	2 (.9)	0 (0)		
Cardiac structural complications				.544 (.09–3.28)	.662
Minor, *n* (%)	0 (0)	0 (0)	0 (0)		
Major, *n* (%)	5 (1.0)	3 (1.4)	2 (.7)		
Unplanned use of MCS, *n* (%)	3 (.6)	1 (.5)	2 (.7)	1.644 (.15–18.26)	1
Newonset or worsened conduction disturbance, *n* (%)	218 (43.6)	98 (43.0)	120 (44.1)	1.047 (.73–1.49)	.799
Newonset AF or flutter, *n* (%)	22 (4.2)	9 (4.1)	13 (4.6)	1.181 (.49–2.81)	.707
New permanent PM implantation, *n* (%)	97 (19.8)	39 (17.7)	58 (21.6)	1.289 (.82–2.03)	.270
Neurological events, *n* (%)	7 (1.3)	5 (2.1)	2 (.7)	.322 (.06–1.68)	.252
Mean aortic valve gradient (mmHg), median (IQR)	8 (5–11)	7 (5–10)	8 (5–11)		.470
LVEF, median (IQR)	60 (55–64)	60 (55–65)	58 (52–60)		**<.001**
PVL ≥ 2, *n* (%)	32 (6.7)	15 (7.0)	17 (6.5)	1.095 (.763–1.571)	.624
Intra-prosthetic aortic regurgitation ≥ 2, *n* (%)	2 (.4)	0 (0)	2 (.8)	1.951 (.498–7.635)	.337
Patient-prosthesis mismatch, *n* (%)	1 (.2)	0 (0)	1 (.4)	.545 (.50–.59)	1

AF, atrial fibrillation; LVEF, left-ventricular ejection fraction; MCS, mechanical circulatory support; PM, pacemaker; PVL, paravalular leak.

disturbance and permanent pacemaker implantation. Regarding echocardiographic parameters at discharge, the median of mean aortic prosthesis gradient was 8 mmHg, with no differences observed between sexes, while LVEF at discharge was higher in women (60 [55–65] vs. 58 [52–60], $P < .001$). Moderate or greater paravalvular leak was detected in 32 patients (6.7%), while moderate or more intra-prosthetic aortic regurgitation occurred in two cases (.4%). Patient-prosthesis mismatch was noted in only one case (.2%), and no cases of late embolization were reported. In-hospital outcomes are summarized in *Table 3*.

Clinical outcomes at 6-month follow-up

At 6 months, all-cause mortality occurred in 20 patients (4.8%), including 17 (4.1%) cardiovascular deaths and one (.2%) valve-related death. There were no significant sex-based differences in all-cause (4.1% women vs. 5.3% men, $P = .685$) or cardiovascular mortality (3.6% vs. 4.4%, $P = .797$).

Device success was achieved in 358 patients (85.2%), with similar rates between females and males (84.6% vs. 85.8%, $P = .252$). Mid-term safety was also comparable between sexes (67.2% vs. 67.1%, $P = .282$). Cardiovascular hospitalizations occurred in 52 patients, with no significant differences between sexes (10.2% vs. 15.0%, $P = .258$). Myocardial infarction and neurological events occurrence were rare (respectively, .7% and 1.2%) and equally distributed between sexes. Acute kidney injury occurred in 4.9% of patients overall (4.9% vs. 5.0%, $P = .613$), while bleeding events requiring intervention or transfusion were reported by 4.0% of patients (5.4% vs. 2.7%, $P = .710$).

Table 4 Six-month clinical outcomes

Variable	Overall (*n* = 420)	Women (*n* = 195)	Men (*n* = 225)	HR (95% CI)	*P*-value
All-cause death, *n* (%)	20 (4.8)	8 (4.1)	12 (5.3)	.860 (.41–1.78)	.685
Cardiovascular death, *n* (%)	17 (4.1)	7 (3.6)	10 (4.4)	.871 (.30–2.49)	.797
Non-cardiovascular death, *n* (%)	2 (.5)	0 (0)	2 (.9)	.731 (.22–2.39)	.606
Bioprosthetic valve dysfunction					.672
Structural complications, *n* (%)	0 (0)	0 (0)	0 (0)		
Non-structural complications, *n* (%)	0 (0)	0 (0)	0 (0)		
Endocarditis, *n* (%)	2 (.5)	0 (0)	2 (.9)		
Thrombosis, *n* (%)	4 (1.0)	2 (1.1)	2 (.9)		
Device success, *n* (%)	358 (85.2)	165 (84.6)	193 (85.8)	.825 (.59–1.15)	.252
Mid-term safety, *n* (%)	282 (67.1)	131 (67.2)	151 (67.1)	.836 (.60–1.16)	.282
Cardiovascular hospitalization, *n* (%)	52 (12.8)	19 (10.2)	33 (15.0)	1.378 (.79–2.40)	.258
Non-cardiovascular hospitalization, *n* (%)	32 (7.9)	14 (7.7)	18 (8.2)	1.004 (.49–2.07)	.991
Myocardial infarction, *n* (%)	3 (.7)	1 (.4)	2 (.9)	1.543 .14–17.05)	.723
Acute kidney injury, *n* (%)	20 (4.9)	9 (4.9)	11 (5.0)	1.737 (.40–4.69)	.613
Bleeding, *n* (%)	13 (4.0)	10 (5.4)	6 (2.7)	.819 (.29–2.35)	.710
Newonset or worsened conduction disturbance, *n* (%)	8 (2.0)	5 (2.7)	3 (1.4)	.819 (.29–2.35)	.710
New onset AF or flutter, *n* (%)	4 (1.0)	1 (.5)	3 (1.4)	1.399 (.23–8.61)	.718
New permanent PM implantation, *n* (%)	5 (1.2)	2 (1.1)	3 (1.4)	.667 (.15–3.03)	.601
Neurological events, *n* (%)	5 (1.2)	2 (1.1)	3 (1.4)	.773 (.16–3.83)	.753
NYHA functional class				.820 (.54–1.26)	.362
I, *n* (%)	244 (67.8)	110 (65.9)	134 (69.4)		
II, *n* (%)	96 (26.7)	48 (28.7)	48 (24.9)		
III, *n* (%)	18 (5.0)	7 (4.2)	11 (5.7)		
IV, *n* (%)	2 (.6)	2 (1.2)	0 (0)		

AF, atrial fibrillation; NYHA, New York Heart Association; PM, pacemaker.

New-onset or worsened conduction disturbance was observed in 2.0% of the cohort, with no statistically significant sex differences (2.7% vs. 1.4%, $P = .710$), while 5 patients required implantation of a permanent pacemaker. Clinical mid-term outcomes are summarized in *Table 4*.

Functional status improved significantly, with most patients classified as NYHA Class I or II. Moderate (NYHA Class III) or severe (Class IV) symptoms were observed in 5% and .6%, respectively. Importantly, no statistically significant differences in residual symptoms post-TAVI were observed between patients with longer versus shorter diagnostic delay, nor between women and men. Kaplan–Meier survival curves for time from symptoms onset to diagnosis and time from diagnosis to TAVI, stratified by sex, showed no significant difference in device success between females and males, indicating comparable temporal patterns across sexes (*Figure 3*). No significant interactions with either sex or country were identified.

Among sex-specific factors, prior gynaecological surgery showed a non-significant trend as a predictor of device success (OR: 2.884 [95% CI: 1.15–7.23], $P = .069$).

Discussion

This study highlights several important findings regarding the diagnosis and management of severe symptomatic AS in patients undergoing TAVI.

The main findings are:

(1) A significant diagnostic delay was observed in women compared with men, with women experiencing a longer median time from symptom onset to clinical diagnosis of severe AS, which was more pronounced in some geographies.
(2) Despite this diagnostic delay, no significant difference was found between sexes in the time from diagnosis to TAVI (therapeutic delay), although notable regional differences were observed across participating centres.
(3) There were no significant sex-related differences in clinical outcomes following TAVI, including technical success, device success and mid-term outcomes at 6 months, as defined by VARC-3 criteria.

Previous studies have reported that in women late diagnosis and delayed referral for AVR are common and associated with poorer prognosis and outcomes.[8] In our study, women experienced longer delays between the onset of symptoms and diagnosis of severe AS than men (median delay of 3 vs. 1 month, $P < .001$), likely resulting from a complex interplay of symptoms under-recognition, differences in symptom reporting and lower rates of seeking medical attention. When stratified by centre, however, a statistically significant sex-based

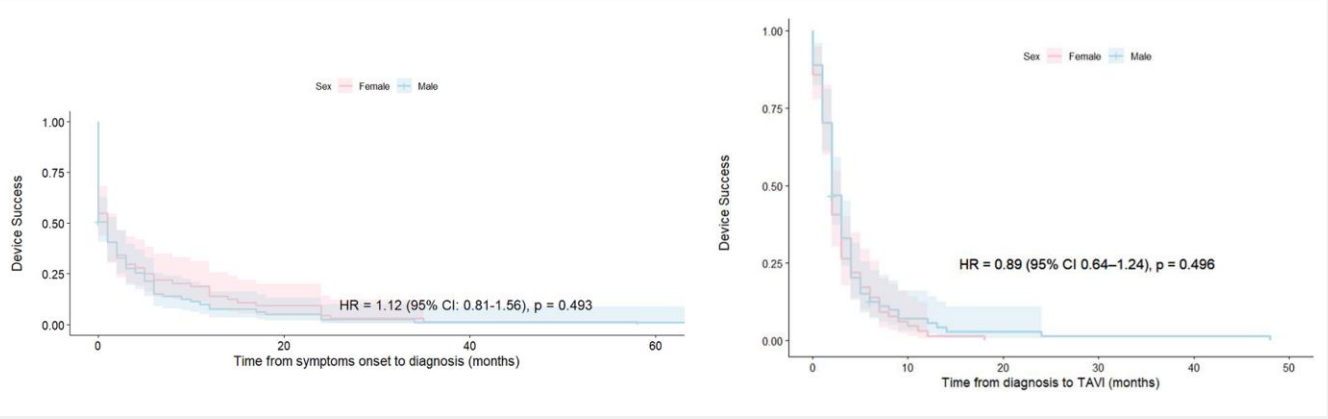


Figure 3 Kaplan–Meier curves depicting device success over time, stratified by sex. Left panel shows device success relative to time from symptom onset to diagnosis. Right panel shows device success relative to time from diagnosis to TAVI. No significant differences in device success between females and males were observed

difference was observed only in Salamanca (median 6 [1–12] months vs. 1 [0–3] month, $P < .001$), suggesting that local organizational or healthcare system factors may contribute to these observed disparities.

Importantly, these delays did not translate into sex-related differences in in-hospital and 6-month clinical outcomes, nor did they independently predict device success or mid-term outcomes after multivariate adjustment. This suggests that, although delays in diagnosis remain a concern, especially among women, they may not directly adversely affect procedural success or clinical outcomes once patients are referred and treated with TAVI. Nevertheless, women presented at a more advanced symptomatic stage and with higher surgical risk, indicating that delayed diagnosis may contribute to pre-procedural disease burden and inequities in access to care.

We also observed a significant inter-centre variation regarding the diagnostic and therapeutic delays. Specifically, patients at the French centre experienced longer median delays compared with those in Italy and Spain, although clinical outcomes were comparable among centres. These differences may reflect system-level differences, such as access to outpatient cardiology services, waiting times for echocardiography or referral pathways to specialized heart teams. However, this finding must also be interpreted in the context of data availability. In Paris, objective clinical documentation of symptom onset was less frequently available, and diagnostic delay was more often estimated based on patient-reported timelines, which are susceptible to recall bias and may lead to overestimation of delay, preferentially representing patients with more memorable and longer diagnostic journeys.

As concerns sex-related disparities, women in this cohort were older, more symptomatic than men, with a higher NYHA functional class and had higher surgical risk profiles, in accordance with published literature.[15,18,19] The advanced symptomatic status of women could be attributed in part to greater echocardiographic AS severity, as indicated by smaller aortic valve areas. Procedural outcomes were similar between sexes, and no significant differences in in-hospital and mid-term clinical outcomes between women and men were detected. While earlier studies have reported higher rates of major vascular complications[20,21] and life-threatening bleeding[22] in women undergoing TAVI, the present study found no statistically significant sex differences in vascular complications or bleeding events, possibly reflecting advances in procedural techniques and operator/centre experience that have improved safety profiles.

With respect to female sex-specific characteristics, no association between the individual female-specific factors collected and VARC-3 outcomes at 6 months was observed in our cohort. These findings suggest that, although women undergoing TAVI may display distinct clinical and biological profiles, there is currently no clear consensus on whether female-specific factors *per se* may independently determine clinical outcomes. Previous studies have shown that, despite higher procedural complication rates, especially vascular, major bleeding and stroke, women experience better survival after TAVI.[23,24] Large registries focusing specifically on women, such as the WIN-TAVI registry, have demonstrated that female-specific characteristics, such as menopausal age, osteoporosis, gynaecological, or breast cancer history, did not appear to be independently associated with VARC-defined endpoints. While women without a history of pregnancy were found to be frailer on the surgical assessment, women with a history of pregnancy had lower rates of the 30-day primary safety endpoint and a tendency for lower occurrence of the 1-year risk of death or stroke.[11,12] Similarly, while an early menopause is associated with increased cardiovascular and all-cause mortality,[25] studies assessing the impact of menopausal age after TAVI have demonstrated no significant differences in adverse events at 1-year follow-up between women with early and regular menopause.[26] Overall, these findings suggest that female-specific factors may influence the pathophysiological and clinical presentation of AS, but do not appear to independently affect outcomes after TAVI.

Finally, while this multicentre analysis provides valuable insight into the sex-related disparities in the timely diagnosis and management of severe AS, its limitations should be acknowledged. The relatively small sample size, particularly for women with detailed sex-specific data, and the incomplete availability of data on AS subtypes and detailed diagnostic intervals (e.g. time from symptom onset to general practitioners referrals, waiting times for echocardiography) may affect generalizability. However, given the higher prevalence of paradoxical LF-LG AS in women, this aspect deserves further investigation in dedicated prospective studies. Future larger-scale investigations are warranted to further explore the impact of sex and female-specific characteristics on AS diagnosis and management and, more broadly, contribute to the understanding of sex-related cardiovascular disorders.

Nevertheless, our findings suggest that to reduce diagnostic delays, efforts should focus on improving earlier symptom recognition and referral. Targeted education of general practitioners and non-cardiology specialists, as well as campaigns of awareness for the general population specifically targeting more fragile patients at higher risk of developing AS and being underdiagnosed, increased awareness of sex-specific symptom presentations, and prompt echocardiographic evaluation may represent the most effective strategies to enhance timely diagnosis and equitable care.

Conclusions

In conclusion, women with severe symptomatic AS experience significantly longer delays from symptom onset to diagnosis, confirming persistent sex-based disparities in timely access to care. These delays may result from a combination of symptoms recognition, reporting differences, or lower healthcare-seeking behaviours among women. Importantly, once diagnosed, procedural success, in-hospital and 6-month clinical outcomes are comparable between sexes. Further research is essential to determine the underlying factors contributing to gender disparities and to reduce these inequalities, ensuring prompt diagnosis and fair and timely treatment for all patients with AS, ultimately improving prognosis and survival.

Author contributions

Angelicarosa Cascone (Data curation [lead]; Formal analysis; Investigation; Visualization [equal]; Writing—original draft [lead]), Francesco Federico (Formal analysis; Investigation; Visualization; Writing—review & editing [equal]), Giulia Ghizzoni (Investigation [equal]; Visualization; Writing—review & editing [supporting]), Ciro Vella (Supervision; Visualization; Writing—review & editing [equal]), Barbara Bellini (Supervision; Visualization [supporting]; Writing—review & editing [equal]), Giulia Botti (Supervision; Visualization [supporting]; Writing—review & editing [equal]), Marco Ancona (Writing—review & editing [supporting]), Luca Ferri (Writing—review & editing [supporting]), Filippo Russo (Writing—review & editing [supporting]), Thomas Lescure (Writing—review & editing [supporting]), Ana Laffond (Writing—review & editing [supporting]), Nicole Karam (Supervision; Writing—review & editing [equal]), Ignacio Cruz Gonzalez (Supervision; Writing—review & editing [equal]), Matteo Montorfano (Supervision; Visualization; Writing—review & editing [equal]), and Alaide Chieffo (Conceptualization; Supervision; Visualization; Writing—review & editing [lead])

Declarations

Data Availability

Information regarding the data is available upon reasonable request.

Disclosure of Interest

BB reports consultant fees from Medtronic. NK reports consultant fees from Abbott, Edwards, and Medtronic. FR reports speaker and consultant fees from Penumbra and Boston Scientific. ICG reports proctor and consultant fees from Edwards, Medtronic, Abbott, and SMT. MM reports consultant fees from Abbott, Boston, Kardia, and Medtronic. AC (Alaide Chieffo) reports speaker consultant fees from Abbott Vasc, Abiomed, Boehringer, Cordis, Penumbra, and Menarini.

Funding

This research received no external funding.

References

1. Goldbarg SH, Elmariah S, Miller MA, Fuster V. Insights into degenerative aortic valve disease. *J Am Coll Cardiol* 2007;**50**:1205–13. https://doi.org/10.1016/j.jacc.2007.06.024
2. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;**368**:1005–11. https://doi.org/10.1016/S0140-6736(06)69208-8
3. Members WC, Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, *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. https://doi.org/10.1016/j.jacc.2020.11.035
4. Praz F, Borger MA, Lanz J, Marin-Cuartas M, Abreu A, Adamo M, *et al.* 2025 ESC/EACTS guidelines for the management of valvular heart disease: developed by the task force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2025;**46**:4635–736. https://doi.org/10.1093/eurheartj/ehaf194
5. Shan Y, Pellikka PA. Aortic stenosis in women. *Heart* 2020;**106**:970–6. https://doi.org/10.1136/heartjnl-2019-315407
6. Masiero G, Paradies V, Franzone A, Bellini B, De Biase C, Karam N, *et al.* Sex-specific considerations in degenerative aortic stenosis for female-tailored transfemoral aortic valve implantation management. *J Am Heart Assoc* 2022;**11**:25944. https://doi.org/10.1161/JAHA.121.025944
7. Lowenstern A, Sheridan P, Wang TY, Boero I, Vemulapalli S, Thourani VH, *et al.* Sex disparities in patients with symptomatic severe aortic stenosis. *Am Heart J* 2021;**237**:116–26. https://doi.org/10.1016/j.ahj.2021.01.021
8. Gjertsson P, Caidahl K, Odén A, Bech-Hanssen O. Diagnostic and referral delay in patients with aortic stenosis is common and negatively affects outcome. *Scand Cardiovasc J* 2007;**41**:12–8. https://doi.org/10.1080/14017430601115935
9. Masiero G, Franzone A, Paradies V, Karam N, Fraccaro C, De Biase C, *et al.* Understanding aortic stenosis and transcatheter aortic valve replacement in women. *Struct Heart* 2025;**9**:100666. https://doi.org/10.1016/j.shj.2025.100666
10. Tribouilloy C, Bohbot Y, Rusinaru D, Belkhir K, Diouf M, Altes A, *et al.* Excess mortality and undertreatment of women with severe aortic stenosis. *J Am Heart Assoc* 2021;**10**:1–13. https://doi.org/10.1161/JAHA.120.018816
11. Chieffo A, Petronio AS, Mehilli J, Chandrasekhar J, Sartori S, Lefèvre T, *et al.* Acute and 30-day outcomes in women after TAVR: results from the WIN-TAVI (women's international transcatheter aortic valve implantation) real-world registry. *JACC Cardiovasc Interv* 2016;**9**:1589–600. https://doi.org/10.1016/j.jcin.2016.05.015
12. Chieffo A, Petronio AS, Mehilli J, Chandrasekhar J, Sartori S, Lefèvre T, *et al.* 1-Year clinical outcomes in women after transcatheter aortic valve replacement: results from the first WIN-TAVI registry. *JACC Cardiovasc Interv* 2018;**11**:1–12. https://doi.org/10.1016/j.jcin.2017.09.034
13. Tchetche D, Pibarot P, Bax JJ, Bonaros N, Windecker S, Dumonteil N, *et al.* Transcatheter vs. surgical aortic valve replacement in women: the RHEIA trial. *Eur Heart J* 2025;**46**:2079–88. https://doi.org/10.1093/eurheartj/ehaf133
14. Hamed O, Persson PJ, Engel AM, McDonough S, Smith JM. Gender differences in outcomes following aortic valve replacement surgery. *Int J Surg* 2009;**7**:214–7. https://doi.org/10.1016/j.ijsu.2009.03.005
15. Fuchs C, Mascherbauer J, Rosenhek R, Pernicka E, Klaar U, Scholten C, *et al.* Gender differences in clinical presentation and surgical outcome of aortic stenosis. *Heart* 2010;**96**:539–45. https://doi.org/10.1136/hrt.2009.186650
16. Clavel MA, Magne J, Pibarot P. Low-gradient aortic stenosis. *Eur Heart J* 2016;**37**:2645–57. https://doi.org/10.1093/eurheartj/ehw096
17. Généreux P, Piazza N, Alu MC, Nazif T, Hahn RT, Pibarot P, *et al.* Valve academic research consortium 3: updated endpoint definitions for aortic valve clinical research. *J Am Coll Cardiol* 2021;**77**:2717–46. https://doi.org/10.1016/j.jacc.2021.02.038
18. Steeds RP, Messika-Zeitoun D, Thambyrajah J, Serra A, Schulz E, Maly J, *et al.* IMPULSE: the impact of gender on the presentation and management of aortic stenosis across Europe. *Open Heart* 2021;**8**:e001443. https://doi.org/10.1136/openhrt-2020-001443
19. Appleby C, Bleiziffer S, Bramlage P, Delgado V, Eltchaninoff H, Gebhard C, *et al.* Sex-related disparities in aortic stenosis from disease awareness to treatment: a state-of-the-art review. *J Thorac Dis* 2024;**16**:6308–19. https://doi.org/10.21037/jtd-24-406
20. Lunardi M, Pighi M, Banning A, Reimers B, Castriota F, Tomai F, *et al.* Vascular complications after transcatheter aortic valve implantation: treatment modalities and long-term clinical impact. *Eur J Cardiothorac Surg* 2022;**61**:934–41. https://doi.org/10.1093/ejcts/ezab499
21. Pighi M, Piazza N, Martucci G, Lachapelle K, Perrault LP, Asgar AW, *et al.* Sex-specific determinants of outcomes after transcatheter aortic valve replacement. *Circ Cardiovasc Qual Outcomes* 2019;**12**:e005363. https://doi.org/10.1161/CIRCOUTCOMES.118.005363
22. van Bergeijk KH, van Ginkel DJ, Brouwer J, Nijenhuis VJ, van der Werf HW, van den Heuvel AFM, *et al.* Sex differences in outcomes after transcatheter aortic valve replacement: a POPular TAVI subanalysis. *JACC Cardiovasc Interv* 2023;**16**:1095–102. https://doi.org/10.1016/j.jcin.2023.02.039
23. O'Connor SA, Morice MC, Gilard M, Leon MB, Webb JG, Dvir D, *et al.* Revisiting sex equality with transcatheter aortic valve replacement outcomes: a collaborative, patient-level meta-analysis of 11,310 patients. *J Am Coll Cardiol* 2015;**66**:221–8. https://doi.org/10.1016/j.jacc.2015.05.024
24. Kodali S, Williams MR, Doshi D, Hahn RT, Humphries KH, Nkomo VT, *et al.* Sex-specific differences at presentation and outcomes among patients undergoing transcatheter

aortic valve replacement: a cohort study. *Ann Intern Med* 2016;**164**:377–84. https://doi.org/10.7326/M15-0121

25. Muka T, Oliver-Williams C, Kunutsor S, Laven JSE, Fauser BCJM, Chowdhury R, *et al.* Association of age at onset of menopause and time since onset of menopause with cardiovascular outcomes. Intermediate vascular traits, and all-cause mortality: a systematic review and meta-analysis. *JAMA Cardiol* 2016;**1**:767–76. https://doi.org/10.1001/jamacardio.2016.2415
26. Edens M, Watanabe Y, Nicolas J, Sartori S, Snyder C, Vogel B, *et al.* Outcomes in patients with early menopause who underwent transcatheter aortic valve implantation. *Am J Cardiol* 2023;**192**:221–7. https://doi.org/10.1016/j.amjcard.2023.01.022