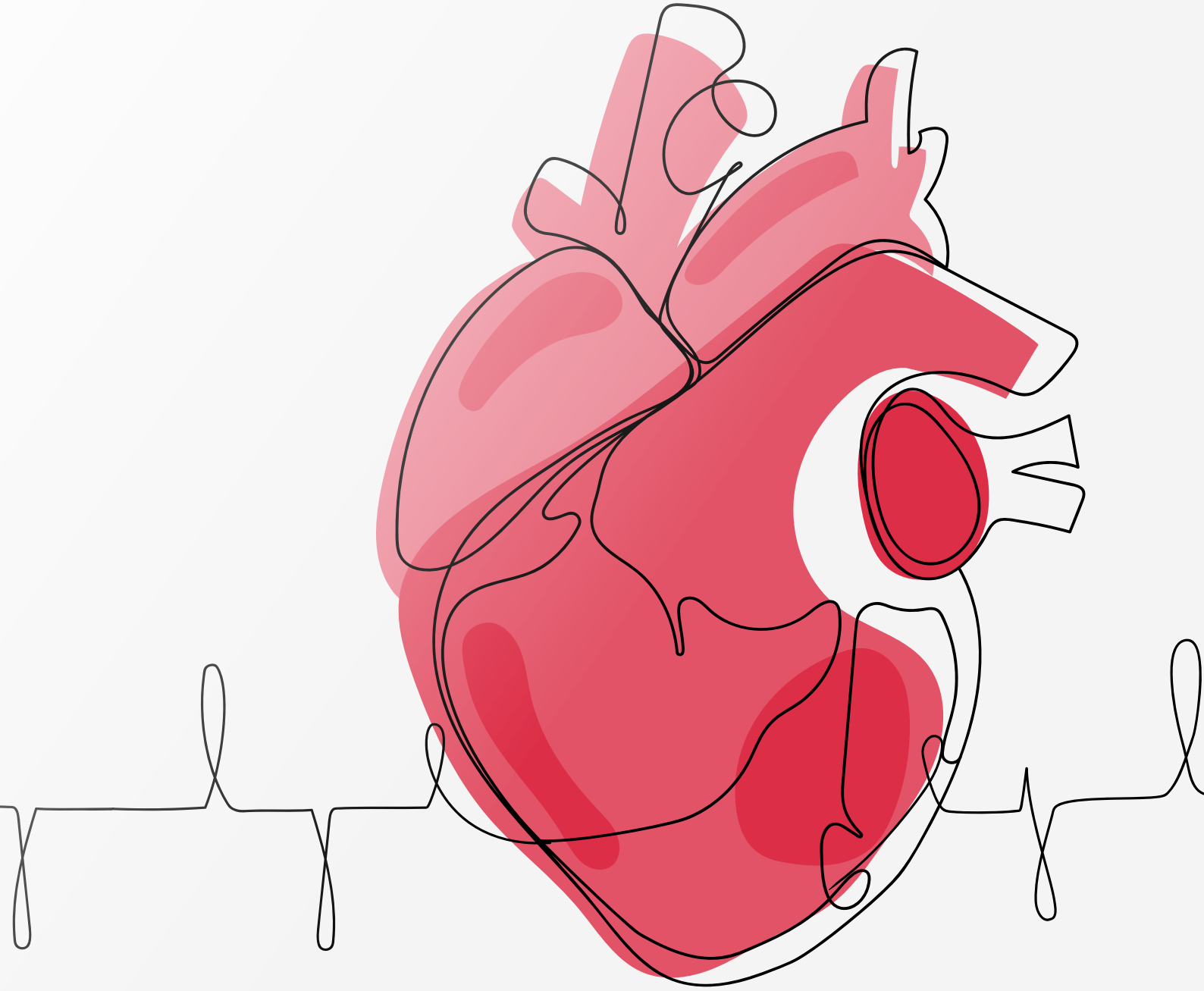
The Beat Goes On

Clinical Insights in Heart Valve Research

Issue 2 – 2024



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Over 1 million severe symptomatic aortic stenosis patients have been treated with TAVR*

***Millions more remain untreated*[1–4]**

You are dedicated to ensuring that patients with symptomatic severe aortic stenosis have access to lifesaving therapy. For the millions of eligible patients still untreated,[1–4] your accurate, early diagnosis and urgent referral to a heart team are crucial.

#ForTheMillionsMore

*Edwards data on file

Introduction

Aortic valve disease remains a critical area of interest in cardiovascular medicine. The landscape of treatment options continues to evolve, and recent research has provided valuable insights into treatment strategies, outcomes and disparities.

As you strive to stay informed about ongoing developments to optimize your patients' care, we present key findings from five pivotal articles. These articles review the spectrum of contemporary care and changing trends.

When emphasizing the need to optimize individualized decision making[5] we are constantly identifying opportunities for improvement in care. This includes both minimally invasive techniques[5] and enhanced postoperative care.

Gender disparities continue to persist in the management of aortic valve disease leading to excess mortality in women.[6] Recognizing and addressing these disparities is paramount for equitable care. Importantly, despite advancements, patients are still not receiving timely referrals for evaluation and care.[7]

As you navigate your clinical practice, consider these updates when evaluating patients with aortic valve disease. By integrating evidence-based insights, we can enhance patient outcomes and bridge gaps in care.

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Senior Director, Clinical Science Liaison
Edwards Lifesciences

Transcatheter or Surgical Treatment of Aortic-Valve Stenosis (DEDICATE Trial)

Blankenberg S *et al. N Engl J Med*. 2024; **390:** 1572–83

Background

Evidence supporting the use of transcatheter aortic valve replacement (TAVR) in younger and lower-risk patients has largely come from industry-sponsored clinical trials in carefully selected patients.[8–12]

However, real-world data comparing the outcomes of TAVR with surgical aortic valve replacement (SAVR) are lacking.[8]

In younger patients (65–80 years of age) at estimated risk not high nor prohibitive, both TAVR and SAVR are indicated in US guidelines,[13] while European guidelines recommend SAVR for younger patients (<75 years of age) at low surgical risk, TAVR for patients of 75 and older at high risk and SAVR or TAVR for all remaining patients.[14]

Aim[8]

To compare outcomes of TAVR and SAVR in patients with severe symptomatic aortic stenosis (sSAS) in a real-world setting.

Study Population[8]

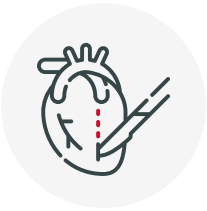
The DEDICATE trial enrolled patients aged ≥65 years with sSAS who were eligible for either TAVR or SAVR, as determined by the multidisciplinary Heart Team. Patients were at low (≤2%) or intermediate (>2% to ≤4%) surgical risk, defined by STS-PROM score.

Patient exclusion criteria included bicuspid valve anatomy, clinically significant coronary artery disease, previous cardiac surgery, and additional concomitant valvular heart disease, among others.

38 centers in Germany
1,414 patients randomized, TAVR = 701 patients, SAVR = 713 patients; median STS score: 1.8%

Final study population[8]*

TAVR group: 683 patients



SAVR group: 613 patients

Primary outcome: Composite of all-cause mortality and fatal or nonfatal stroke within 1 year of randomization.

Secondary outcomes: Included individual components of the primary endpoint, acute kidney injury, arrhythmia and pacemaker implantation, bleeding, myocardial infarction, prosthetic valve dysfunction, rehospitalization, and vascular complications.

*Some reasons for the drop-off from randomization totals included patient withdrawal from study, ineligibility discovery, treatment crossover, or death before completion

Results[8]

Table 1. Primary outcome and secondary outcomes at 1 year*

Outcome, n (%)	TAVR N=701	SAVR N=713	Hazard ratio (95% CI)
Primary endpoint			
All-cause mortality or stroke†	37 (5.4)	68 (10.0)	0.53 (0.35–0.79)
Secondary endpoints			
All-cause mortality	18 (2.6)	42 (6.2)	0.43 (0.24–0.73)
Stroke	20 (2.9)	32 (4.7)	0.61 (0.35–1.06)
Stroke or TIA	28 (4.1)	35 (5.1)	0.78 (0.47–1.27)
Disabling stroke	9 (1.3)	21 (3.1)	0.42 (0.19–0.88)
Death from any cause or disabling stroke	26 (3.8)	57 (8.4)	0.45 (0.28–0.70)

*The analyses were stratified according to the STS-PROM score. The percentage of patients was calculated as a Kaplan–Meier estimate
The 95% confidence intervals have not been adjusted for multiplicity and should not be used to make hypothesis-test inferences about superiority or noninferiority

†p<0.001 for the primary analysis

CI: confidence interval; SAVR: surgical aortic valve replacement; STS-PROM: Society of Thoracic Surgeons predicted risk of mortality; TAVR: transcatheter aortic valve replacement; TIA: transient ischemic attack

The Kaplan–Meier estimate for the primary outcome in the intention-to-treat population was 5.4% for TAVR and 10.0% for SAVR, demonstrating that TAVR is noninferior to SAVR (p<0.001 for noninferiority). Annual rates for the primary outcome and the majority of the secondary outcomes were lower for TAVR than SAVR.

Subgroup analyses of the primary outcome

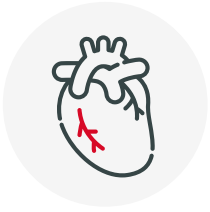
Age

Sex

Surgical risk (STS PROM)

Comorbidities‡

Body mass index



Left ventricular ejection fraction

To view the full forest plot, please visit: https://www.nejm.org/doi/10.1056/NEJMoa2400685

‡Comorbidities included: coronary artery disease, previous myocardial infarction, previous stroke, cerebrovascular disease, peripheral vascular disease, and chronic obstructive pulmonary disease

STS-PROM: Society of Thoracic Surgeons predicted risk of mortality

Conclusion[8]

TAVR was noninferior to SAVR for the primary outcome of all-cause death or fatal or non-fatal stroke at 1 year. Additionally, the annual incidence rates of the primary and most of the secondary outcomes were lower for patients who underwent TAVR compared with those who underwent SAVR. This study was designed to assess outcomes of TAVR versus SAVR outside the limited criteria of typical clinical trials. Patients were deemed eligible based on local multidisciplinary Heart Team evaluation, with valve choice at the operator's discretion, reflecting real-world treatment.

Clinical Insights[8]

- TAVR is an effective option for many low- and intermediate-risk patients with sSAS.
- TAVR is noninferior to SAVR regardless of valve selection or patient management.
- This study adds to the growing body of evidence that supports partnering with a multidisciplinary Heart Team for patient evaluation and prosthesis selection.

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Examining Lack of Referrals to Heart Valve Specialists as Mechanisms of Potential Underutilization of Aortic Valve Replacement

Etiwy M *et al*. *Am Heart J*. 2024; **274:** 54–64

Background

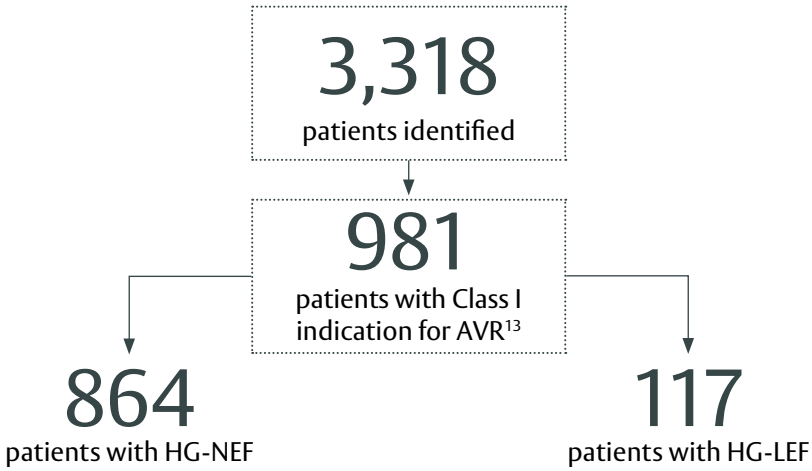
Many patients with severe aortic stenosis (SAS) remain untreated,[7] despite guidelines recommending intervention in both symptomatic and Class I asymptomatic patients on the recommendation of the Heart Team.[13,14] The reasons for undertreatment of SAS may include under-recognition of patients who may benefit from aortic valve replacement (AVR), recognition of patients who may benefit from AVR but are not referred, and appropriate under-referral of patients who do not consent to AVR, or who have contraindications or competing comorbidities.[7]

Aim[7]

To identify the reasons for under-referral of patients with symptomatic SAS and identify areas for clinical practice improvement.

Study Population[7]

All patients who underwent a transthoracic echocardiogram (TTE) and were diagnosed with SAS within the Mass General Brigham Healthcare system in the United States between January 2015 and December 2018 were included.



HG-LEF: high gradient and low left ventricular ejection fraction (LVEF) (mean gradient ≥40 mmHg; LVEF <50%); HG-NEF: high gradient and normal LVEF (mean gradient ≥40 mmHg; LVEF ≥50%).

The medical records of all patients with an indication for intervention but who did not undergo AVR within **1 year** of their TTE were retrospectively reviewed by a single physician and pre-specified clinical information was extracted, including:

1. Determining whether the patient was evaluated by a Heart Team within 6 months of their TTE
2. Identifying any reasons for not proceeding with AVR
3. Documenting the medical specialty of the evaluating clinician

Results[7]

Of the 981 patients who met the criteria for AVR:

790 (80.5%)
were evaluated by a heart valve specialist within 6 months of their TTE

677 (69%)
underwent AVR within 1 year:
311 (46%) surgical
366 (54%) transcatheter

74.8 ± 82.5
days mean time from TTE to AVR

Patients referred to heart valve specialists were younger (76.1 ± 10.8 years *vs* 80.5 ± 12.4 years), more likely to be married (52% *vs* 39.3%), higher hematocrit (37.2 ± 5.6% *vs* 33.1±6.0%), higher estimated glomerular filtration rate 62.8 ± 23.0 mL/min/1.73m^2 *vs* 57 ± 25.5 mL/min/1.73m^2), lower incidence of inpatient TTE (35.8% *vs* 67.5%), and higher mean aortic valve gradient (53.7 ± 12.8 mmHg *vs* 50.2 ± 10.4 mmHg) than patients not referred to a heart valve specialist.

While the probability of survival between referred and non-referred patients was equal at the time of their TTE, it rapidly decreased in patients not referred to a heart valve specialist (Figure 1).

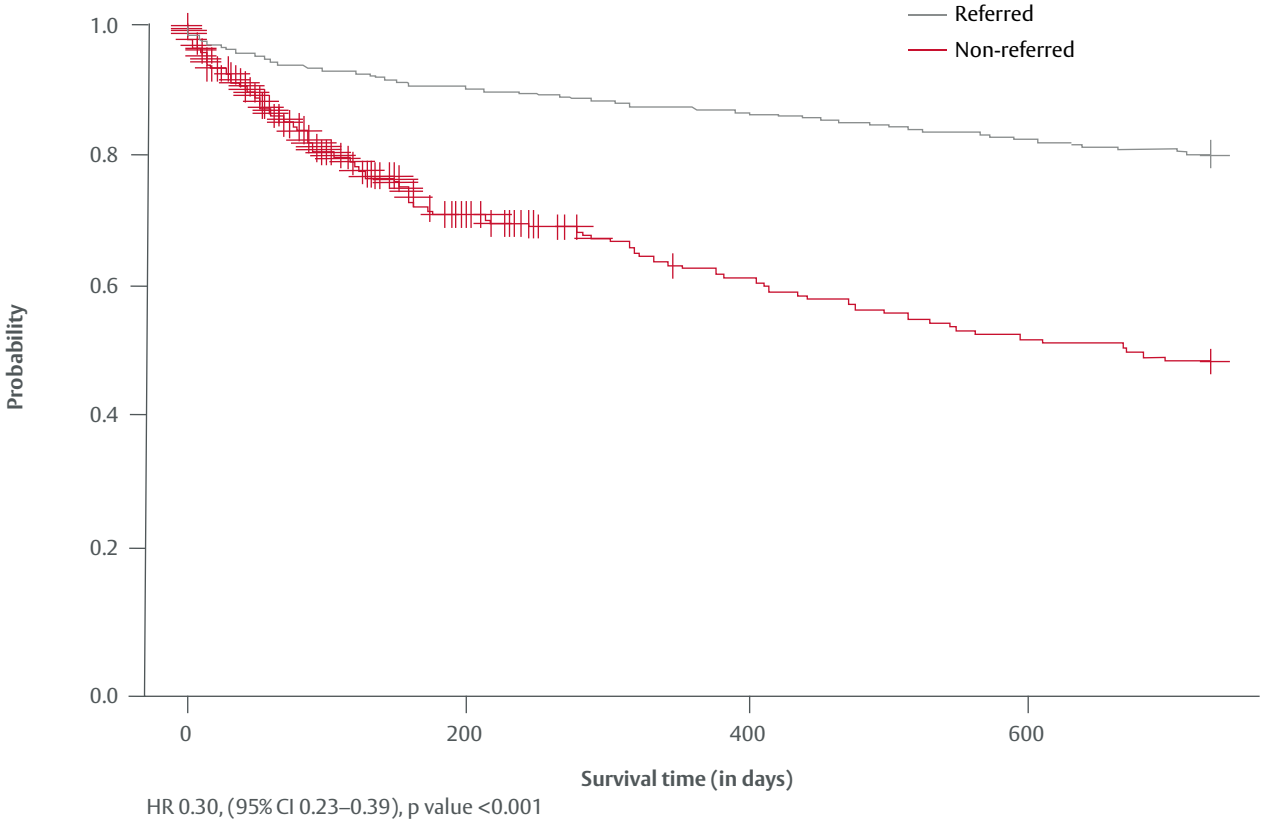
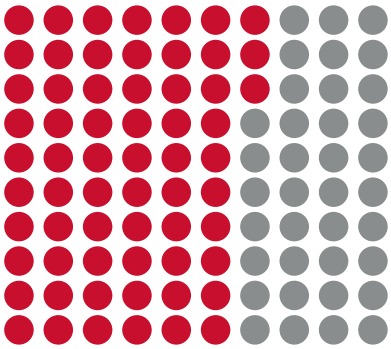


Figure 1. Comparative analysis of heart valve specialist referrals in SAS with a Class I indication for AVR: Referred versus non-referred patients

Reprinted from *American Heart Journal*. 2024; 274, Etiwy M *et al*, Examining Lack of Referrals to Heart Valve Specialists as Mechanisms of Potential Underutilization of Aortic Valve Replacement, pages 54–64, Copyright (2024), with permission from Elsevier.
AVR: aortic valve replacement; CI: confidence interval; HR: hazard ratio

Referral to a Heart Team



63% of patients who did not undergo AVR were not evaluated by a Heart Team within 6 months of their TTE

Of the 304 patients who did not undergo AVR within 1 year of their TTE, only 113 (37.2%) were evaluated by a heart valve specialist within 6 months of their TTE.

Of the 981 patients with a Class I indication for AVR, 191 (19.5%) were not referred to a heart valve specialist, with reasons for not referring including: patients considered too high risk, patients lost to follow-up, patient refusal, and symptoms not attributed to aortic stenosis.

Conclusion[7]

Nearly 20% of patients with a Class I indication for AVR were not assessed by a heart valve specialist within 6 months of their TTE. These data demonstrate that patients who are not referred to a heart valve specialist face a significantly increased mortality risk, especially from 6 months up to 2 years.

The difference in mortality in this study is larger than the reported outcomes of clinical trials, which may be due to selection bias as healthier patients were more likely to be referred. This difference may also be related to the evaluation by the heart valve specialist, as more referred patients underwent AVR.

Creating patient tracking registries can help ensure that referred patients with SAS receive timely evaluations. Additionally, utilizing available shared decision-making tools can assist healthcare providers in ensuring their patients receive the care and outcomes they deserve.

Clinical Insights[7]

- Patients who are not referred to multidisciplinary Heart Teams are more likely to have poor outcomes.
- Patients who would benefit from AVR are often under-recognized, their symptoms are under-appreciated, or they are not referred due to the lack of shared decision making or potential comorbidities.
- A heart valve specialist evaluation may lead to more patients receiving appropriate treatment for their SAS.
- Referring patients for an AS evaluation with a Heart Team ensures evidence-based decision making and may reduce the number of patients lost to follow-up or determined to be too high-risk, and can increase the correct identification of symptoms not originally attributed to AS.

Feature Article

Aortic Valve Replacement Today: Outcomes, Costs, and Opportunities for Improvement

Amin S *et al*. *Cardiovasc Revasc Med*. 2024; **64:** 78–86

The growth of TAVR

Here, Amin *et al*. review the growing body of evidence and consider how to address the undertreatment of patients with severe symptomatic aortic stenosis (sSAS).[5] The benefits of transcatheter aortic valve replacement (TAVR) have been demonstrated across all surgical risk categories.[10, 15, 16] As a result, TAVR has now overtaken surgical aortic valve replacement (SAVR) in the US as the most common treatment for severe aortic stenosis (SAS) (Figure 1).[17] Valve durability and patient life expectancy must be factored in when deciding on an intervention, as patients may outlive their initial bioprosthesis. Other key factors to consider include comorbidities, patient preference, the potential for future coronary access, and the risk of long-term pacemaker implantation.[5]

Over the last decade, TAVR patients have seen improvements in clinical outcomes. These include shorter hospital stays, lower 1-year mortality rates, and a decline in stroke risk. Moreover, an increasing number of patients are being discharged home instead of to rehabilitation or nursing facilities (Table 1).[5]

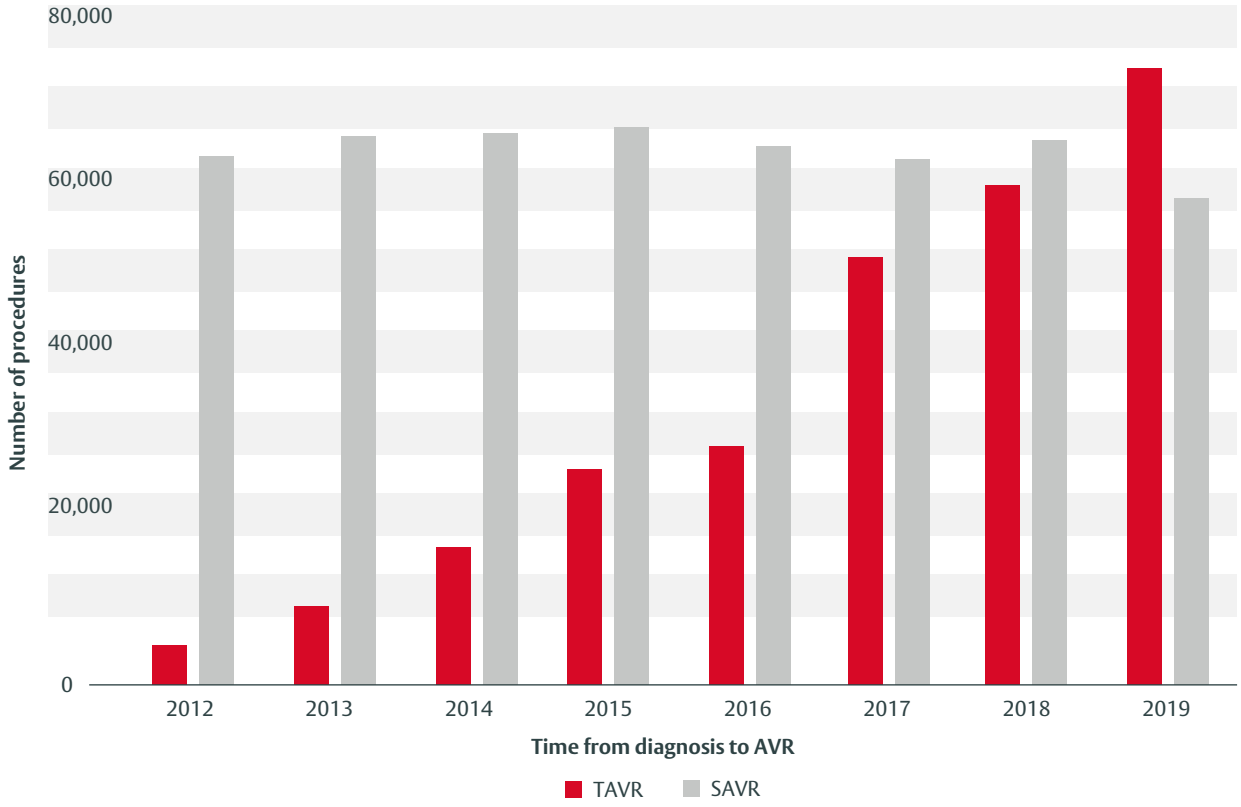


Figure 1. Annual volumes of TAVR and SAVR, adapted from Carroll JD *et al*.

Table 1. TAVR: Changes in patient characteristics and outcomes over time[5]

	Before 2013 (N=13,723)	2019 (N=72,991)
Age, median, years	84	80
STS-PROM, median, %	6.9	4.4
Length of stay, median/patient, days	7.0*	2.0
1-year mortality, %	18.1	10.2
Non-fatal stroke, % In-hospital 30-day	 2.1 2.5	 1.6 2.1
Discharge to home, %	62.4	90.3

STS-PROM: Society of Thoracic Surgeons predicted risk of mortality; TAVR: transcatheter aortic valve replacement
* in 2013 only

Undertreatment of SAS

Despite increasing numbers of aortic valve replacement (AVR) AVR procedures, undertreatment of SAS remains a concern.[5] In a study of 6,150 patients with SAS and a clear indication for AVR (based on US 2014 guidelines), just 48% received an AVR within 2 years of their transthoracic echocardiogram (TTE) . Importantly, almost 1 in 3 patients with a Class I recommendation had not recieved AVR within 2 years.[18]

Patients who did not undergo AVR were more likely to be older, have less coronary artery disease, have lower hematocrit, have low-gradient, low-flow SAS, and have had their TTE performed in an inpatient setting.[18]

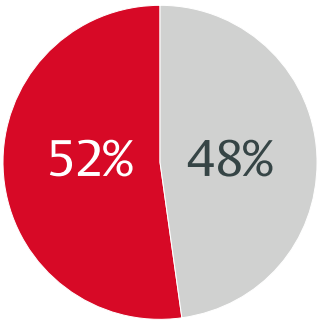
Delaying referral to a multidisciplinary Heart Team may increase the risk of mortality, myocardial infarction, and post-TAVR complications due to congestive heart failure.[5]

49% of patients with SAS **were not referred** to a Heart Team

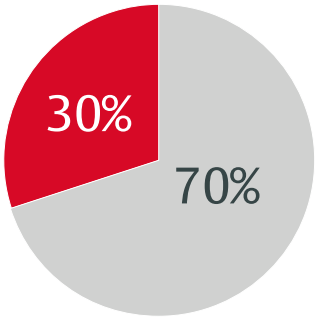
Reasons for under-referral included[23]:

- General cardiologist belief that symptoms were not caused by aortic stenosis/patient was asymptomatic
- TTE report was ambiguous and did not definitively characterize the degree of aortic stenosis
- Patient preference

Percentage of patients receiving AVR within 2 years of their TTE



Patients with clear indication for AVR



Patients with high-gradient severe AS and a Class I indication for AVR

treated untreated

Improve access to AVR

Undertreatment of patients with SAS has highlighted an urgent need to improve access to AVR. Several key opportunities have been identified, including:[5]

Perform a TTE[5]

Perform an exercise stress test to identify symptoms in patients who appear asymptomatic[13]

Refer patients to a multidisciplinary Heart Team early[5]

Improve communication with patients and healthcare professionals at every stage of the treatment pathway, including diagnosis and referral[5]

Involve patients' families in the evaluation of symptoms – family members may be more likely to recognize changes in exercise capacity and dyspnea over time[5]

Increase surveillance in patients in demographic groups associated with lower levels of diagnosis and treatment[5]

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Benefits of TAVR

Cost-effectiveness

Despite the higher prosthesis cost, TAVR becomes cost-saving at 2 years after the procedure due to significant reductions in hospital length of stay and resource use compared with SAVR.[19]

TAVR is cost-effective compared with SAVR in patients at all levels of surgical risk. The long-term cost-effectiveness of TAVR versus SAVR is dependent on mortality rates, which could be affected by valve durability.[5] Current data on low risk patients suggest that transcatheter valves have similar or better freedom from structural valve deterioration up to 5 years.[11]

Real-world data also demonstrate the cost-effectiveness of TAVR versus SAVR at 1-year follow-up across all risk groups, with a reduction in the costs of index hospitalization across all risk groups driven by the reduction in length of stay.[20]

Minimalist TAVR pathways may further reduce the length of hospital stay. In that study, more than 80% were discharged on the same day (n=114 of 516) or next day (n=329 of 516) following TAVR, and same-day discharge did not impact safety outcomes compared with next-day discharge.[21]

Cost through 2 years follow-up:[19]

p=0.31

TAVR: $66,834
SAVR: $68,864

Total length of stay:[19]

p<0.001

TAVR: 1.9 days
SAVR: 6.5 days

Intensive care unit stay:[19]

p<0.001

TAVR: 0.8 days
SAVR: 2.7 days

Conclusion[5]

Despite the increase in AVR procedures, undertreatment of patients with an indication for AVR remains an issue. Early diagnosis and referral to a Heart Team may increase the utilization of this vital intervention. While the choice of intervention for individual patients should consider anatomic factors, comorbidities, life expectancy, and patient preference, the clinical and economic benefits of TAVR over SAVR have been demonstrated across all surgical risk groups. Longer-term data will further inform decision making.

Clinical Insights

- Exercise testing and involving patients' families in the assessment of AS symptoms may increase the diagnosis of sSAS.[5,13]
- Prompt referral to the Heart Team increases the likelihood of patients receiving timely AVR, avoiding the poor outcomes associated with untreated SAS.[5]
- Despite higher prosthesis costs, TAVR is emerging as the economically optimal treatment choice over SAVR and medical management.[22]

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Excess Mortality and Undertreatment of Women with Severe Aortic Stenosis

Tribouilloy C *et al*. *J Am Heart Assoc*. 2021; **10:** e018816

Background[6]

Although females represent half of the aortic stenosis (AS) population, the impact of sex on presentation, management and outcomes in patients with AS is still unclear. Additionally, despite increasing awareness of differences in the pathophysiology of AS in men and women, the relationship between these clinical differences and disease remains poorly defined.

Aim[6]

To evaluate:

1. 5-year mortality by sex
2. 5-year mortality by sex in age-matched patients
3. Timing and use of aortic valve replacement (AVR) by sex, before and after age matching
4. 5-year mortality by sex after AVR

Study Population[6]

Consecutive patients aged at least 18 years, who were diagnosed with severe aortic stenosis (SAS) (aortic valve area [AVA] <1 cm^2 or indexed AVA <0.6 cm^2/m^2) between 2000 and 2017 were included.

Clinical and baseline characteristics, including cardiovascular risk factors, presence of symptoms, comorbidities, and presence of coronary artery disease, were retrospectively recorded.

Primary endpoint: 5-year all-cause mortality.

Secondary endpoints: AVR performance and 5-year survival post AVR (early and late).*

Age matching: Each male patient was matched to a female patient with a caliper width of 0.1 year of age. Determinants of early AVR were analyzed in the overall study population by classical multivariate logistic regression analysis.†

*Early AVR is defined as AVR performed within 3 months of inclusion. Perioperative mortality defined as death occurring within 30 days of AVR or during hospitalization, if the patient was hospitalized for a longer period of time.

†After adjustment for age, symptoms, hypertension, Charlson comorbidity index (not including age), atrial fibrillation, coronary artery disease, AVA, mean pressure gradient, and left ventricular ejection fraction; and in the age-matched population by conditional multivariate logistic regression analysis after adjustment to the same variables (except age).

Results[6]

Baseline characteristics

Compared with men, women:

- were diagnosed at a later age
- had fewer comorbidities
- had a higher symptom burden
- had similar gradients and indexed AVA
- had a higher left ventricular ejection fraction

With this, women were managed conservatively for longer and underwent AVR less frequently than men (Table 1).

Table 1. Management of patients with SAS

Variables	Male (N=1,251)	Female (N=1,178)	p value	Hochberg adjusted p value
AVR, n (%)	863 (69.0)	484 (58.9)	<0.001	<0.016
Early AVR, n (%)	601 (48.0)	494 (41.9)	0.001	0.016
Time to AVR, months	14 ± 23	16 ± 25	0.030	0.270
Combined procedures, n (%)*	204 (23.2)	150 (21.3)	0.200	0.530

*Coronary bypass and/or ascending aorta replacement
AVR: aortic valve replacement; SAS: severe aortic stenosis

5-year survival

Estimated 5-year survival was 69 ± 1% for males and 62 ± 2% for females. The 5-year relative survival was 97% in males, but only 87% in females (Figure 1).

Figure 1. Five-year estimated and observed survival of male and female patients with AS, compared with that of age- and sex-matched general population

Conclusion[6]

Women were diagnosed at a later age than men, despite having similar AS severity and a higher symptom burden. Importantly, even after age matching, women with SAS experience higher mortality rates than men, despite women's longer life expectancy in the general population.

Furthermore, women are less frequently and later indicated for AVR compared to men. Investigating the link between conservative management of women and their increased mortality rate is crucial to address this imbalance.

Clinical Insights[6]

- Recognizing symptoms of AS in females can be challenging. It is important to increase awareness of how AS presents differently in women to ensure timely diagnosis.
- Prospective studies are needed to clarify the reasons for operative or conservative management; these will aid the development of specific corrective measures to address the treatment differences between males and females.
- The disparities in treatment and outcome of SAS between the sexes need to be addressed and should, therefore, be brought to the attention of the cardiology community to ensure prompt consideration.

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Notes

Edwards Lifesciences planned exhibits at upcoming cardiac conferences

Have questions about aortic stenosis or TAVR outcomes? Visit Edwards at these conferences:

AHA	**November 16–18, 2024:** Chicago, IL, USA
PCR London Valves	**November 24–26, 2024:** London, UK
SCAI Fall Fellows	**December 13–17, 2024:** Miami, FL, USA
STS	**January 24–26, 2025:** Los Angeles, CA, USA
Tokyo Valves	**February 7–9, 2025:** Tokyo, Japan
CRF	**February 28–March 1, 2025:** New York, NY, USA
JCS	**March 8–10, 2025:** Kobe, Japan
ACC	**March 28–30, 2025:** Chicago, IL, USA
SCAI	**May 1–3, 2025:** Washington, DC, USA
AATS	**May 2–5, 2025:** Seattle, WA, USA
EuroPCR	**May 20–23, 2025:** Paris, France
New York Valves	**June 25–27, 2025:** New York, NY, USA
CSANZ	**August 13–17, 2025:** Brisbane, Australia
ESC	**August 28–September 1, 2025:** Madrid, Spain
JCC	**September 19–21, 2025:** Kochi, Japan
TCT	**October 25–28, 2025:** San Francisco, CA, USA

Find out more

Scan the QR codes below to access the original publications:

Transcatheter or Surgical Treatment of Aortic-Valve Stenosis (DEDICATE Trial)

Blankenberg S *et al. N Engl J Med.* 2024; **390:** 1572–83

Examining Lack of Referrals to Heart Valve Specialists as Mechanisms of Potential Underutilization of Aortic Valve Replacement

Etiwy M *et al. Am Heart J.* 2024; **274:** 54–64

Feature article: Aortic Valve Replacement Today: Outcomes, Costs, and Opportunities for Improvement

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Tribouilloy C *et al. J Am Heart Assoc.* 2021; **10:** e018816

Any Edwards LIfesciences support, financial or otherwise, for the studies cited above is disclosed in the associated publication.

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Abbreviations:

AS:	aortic stenosis
AVA:	aortic valve area
AVR:	aortic valve replacement
CI:	confidence interval
HG-NEF:	high gradient and normal left ventricular ejection fraction
HG-LEF:	high gradient and low left ventricular ejection fraction
HR:	hazard ratio
HVS:	heart valve specialist
LVEF:	left ventricular ejection fraction
SAS:	severe aortic stenosis
SAVR:	surgical aortic valve replacement
sSAS:	severe symptomatic aortic stenosis
STS-PROM:	Society of Thoracic Surgeons predicted risk of mortality
TAVR:	transcatheter aortic valve replacement
TTE:	transthoracic echocardiogram

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