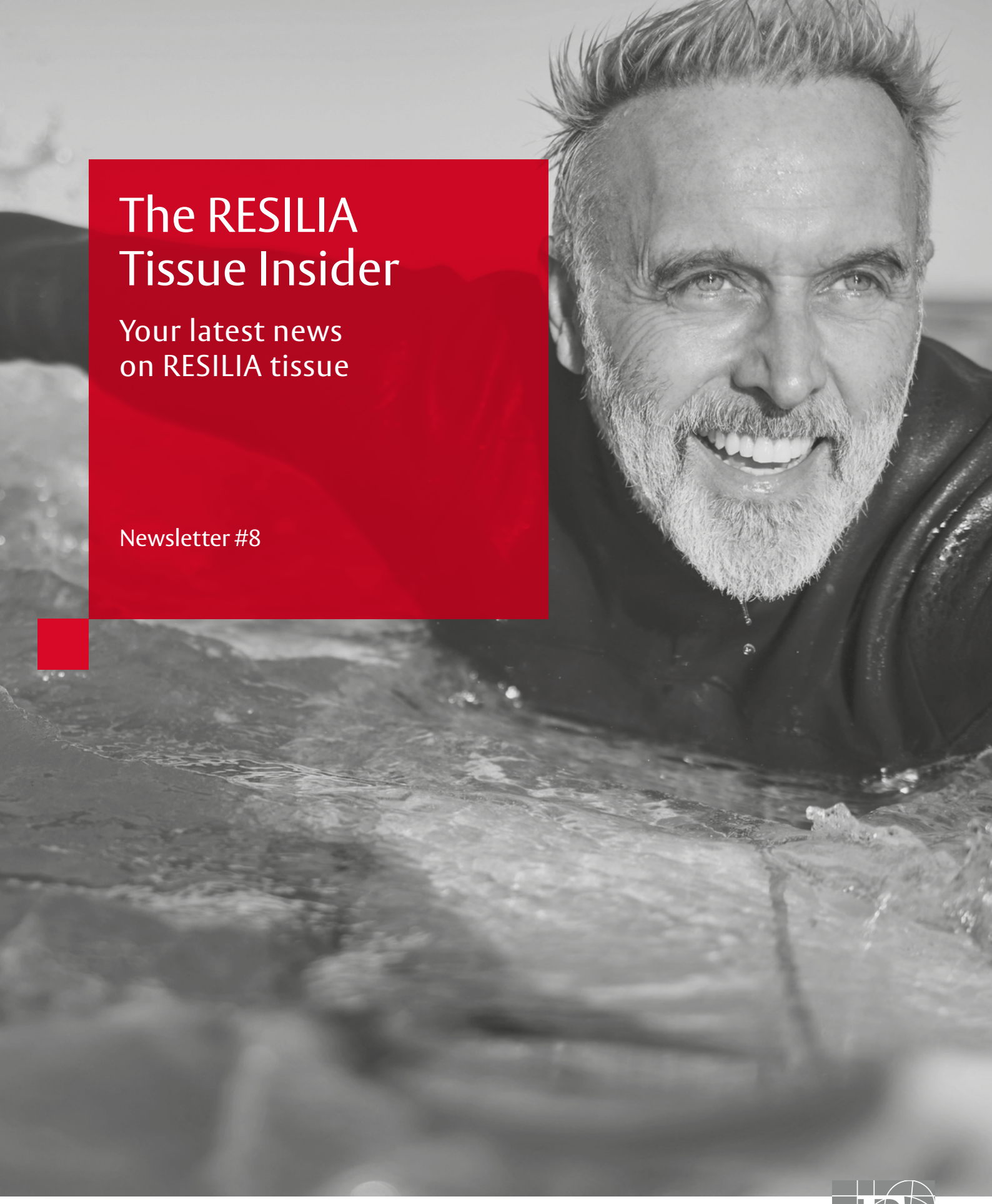


The RESILIA Tissue Insider

Your latest news on RESILIA tissue

Newsletter #8

Edwards

Over 250,000 hearts have been treated with INSPIRIS RESILIA aortic valves worldwide

Get closer to valve therapy.
Get closer to innovation.

In this issue

FRONT COVER IMAGE:
ISTOCK.COM/PEOPLEIMAGES

Introduction

In this issue, we share that more than 250,000 patients have now received an INSPIRIS RESILIA aortic valve, potentially offering them a long-lasting valve that does not limit their future treatment options. Turn to page 4 for the features of the INSPIRIS RESILIA valve and lifetime management options for your patients.

Recent congress highlights include 3-year data on the INSPIRIS RESILIA valve in younger patients, presented at the SFCTCV meeting (page 5), and a merged analysis of the outcomes for bicuspid *versus* tricuspid valve morphologies from the IMPACT and INDURE registries, presented at the ÖGTHG meeting, on page 7.

Data continue to emerge from the COMMENCE aortic trial, with subgroup analyses of the 5-year outcomes. Promising results for patients with mixed aortic valve disease (MAVD) or bicuspid aortic valves (BAV) were presented at the AATS Annual Meeting in April and published in *The Annals of Thoracic Surgery*, respectively. We summarise their findings on pages 8 and 9.

Finally, Dr Patrick Klein shares his insights on how the INSPIRIS RESILIA valve has impacted his surgical approach and shared decision making.

Enjoy reading!

We hope you enjoy this issue of *The RESILIA Tissue Insider*. Learn more about how the INSPIRIS RESILIA aortic valve could facilitate the lifelong management of your patients' aortic valve disease: scan the QR code to visit our website.

Edwards' latest valve innovations in Europe powered by RESILIA tissue technology

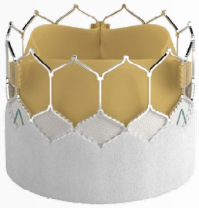
Our commitment to innovation continues as we further expand the **RESILIA tissue portfolio**, with the transcatheter SAPIEN 3 Ultra RESILIA valve now available in Europe.

Surgical valves

MITRIS RESILIA mitral valve

INSPIRIS RESILIA aortic valve

Transcatheter valve



SAPIEN 3 Ultra RESILIA valve

The INSPIRIS RESILIA aortic valve: Closer to valve therapy. Closer to your patients

Patients with aortic valve disease seek a durable solution that reduces the burden on their day-to-day life.[1] Valve selection is a lifelong commitment that requires careful consideration of valve durability and its impact on possible secondary interventions.[2]

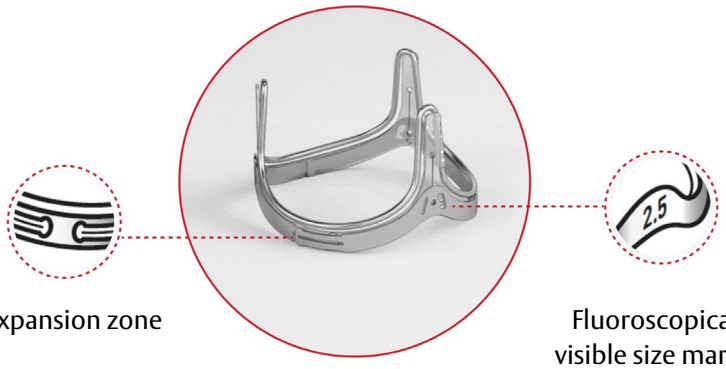
Patients are increasingly turning to bioprosthetic valves, away from mechanical valves, to avoid lifelong anticoagulation and the associated risk of bleeding.[3–5] Irrespective of the choice of bioprosthesis, some patients may require a second intervention. With life expectancy on the rise,[6] patients need a durable valve that facilitates future treatment options.[2]

The INSPIRIS RESILIA valve could help manage your patients' aortic valve disease over a lifetime.[7,8]

The INSPIRIS RESILIA valve was designed with the potential to offer your patients a long-lasting tissue valve, featuring an expandable frame to open up potential future treatment options.[7,8]

The INSPIRIS RESILIA valve is the market-leading surgical replacement aortic tissue valve and, to date, has been implanted in 250,000 patients worldwide.

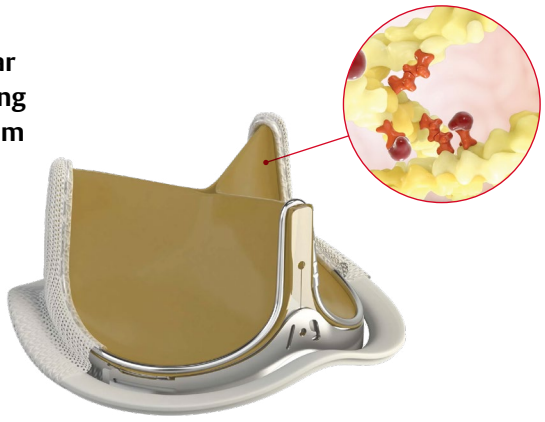
VFit technology is designed to enable potential future valve-in-valve procedures by delivering a controlled and predictable expansion during valve-in-valve deployment.[7,a,b]



[a]Based on bench data during design verification testing.
[b]Refer to device instructions for important warnings related to VFit technology. These features have not been observed in clinical studies to establish the safety and effectiveness of the model 11500A for use in valve-in-valve procedures. VFit technology is available on sizes 19–25 mm.

RESILIA tissue is designed with valve durability in mind, featuring enhanced anticalcification properties and dry storage.[7,8,a]

Scan the QR code to explore the molecular mechanism underlying our innovative calcium blocking technology.



[a]No clinical data are available that evaluate the long-term impact of RESILIA tissue in patients. Additional clinical data for up to 10 years of follow-up are being collected to monitor the long-term safety and performance of RESILIA tissue.

The INSPIRIS RESILIA valve provides a confident foundation for your patients' futures.

RESILIA tissue is backed by a growing track record of clinical evidence.[9–11] Find out about the latest clinical evidence supporting the use of the INSPIRIS RESILIA valve by scanning this QR code.

Congress highlights: RESILIA tissue at SFCTCV, ÖGHTG and AATS

Three-year follow-up of the INSPIRIS RESILIA valve in the aortic position

Aupart A. Presented at SFCTCV meeting, 12–14 June 2024, Nancy, France.[12]

At the SFCTCV meeting, Dr Aupart presented 3-year follow-up data from a French multicentre study of 771 patients undergoing aortic valve replacement (AVR) with an INSPIRIS RESILIA valve from June 2017 to December 2023. Mean age was 60 ± 9 years (range 20–90 years), 35% of patients were female, and mean EuroSCORE II was 2.9%.[12]

Ultrasound was carried out at 6 months and 1 year following AVR, and yearly thereafter, with scans performed if subclinical thrombosis was a concern. At 3-year follow-up, mean gradient was 12.4 mmHg, and effective orifice area (EOA) was 1.79 cm^2. Of the 771 patients who underwent AVR, structural valve deterioration (SVD) was seen in seven patients (0.9%), all of whom underwent redo surgical AVR (SAVR) or valve-in-valve transcatheter aortic valve implantation (TAVI). Subclinical thrombosis was seen in nine patients (1.2%) and was treated with anticoagulation. Freedom from mortality was 94.1% at 3 years, and freedom from SVD was 98.3%.[12]

In this study, the SVD rate was low, but not zero, at 3 years, highlighting the importance of regular monitoring in younger patients.[12] Additionally, the rate of subclinical thrombosis is in accordance with EU recommendations to use oral anticoagulant or antiplatelet agents for the first 3 months following AVR.[13] Although further study is needed, these data suggest that the INSPIRIS RESILIA valve is a useful addition to the bioprosthetic valve portfolio.[12]

Congress highlights: RESILIA tissue at SFCTCV, ÖGHTG and AATS

Durability of the INSPIRIS RESILIA aortic valve in Paris hospitals – ENDURANCE registry

Fiore A *et al.* Presented at SFCTCV meeting, 12–14 June 2024, Nancy, France.[14]

The INSPIRIS RESILIA valve presents an opportunity to reduce the risk of SVD, particularly in younger patients. At the SFCTCV meeting, Fiore *et al.* presented early haemodynamic, safety and durability data from a prospective, multicentre registry.[14]

A total of 1,208 consecutive patients who underwent AVR with the INSPIRIS RESLIA valve between 2019 and 2023 were included; mean age was 63.2 ± 9.9 years, 76.5% were male, and mean EuroSCORE II was 4.8 ± 7.5%.[14]

At 1-year follow-up:

94.6% Survival

2.7% Rate of stroke

2.5% Pacemaker implantation rate

Mean gradient was 10.6 mmHg, and mean EOA was 2.3 cm^2 at 1 year. Patient–prosthesis mismatch was seen in nine patients, with one case of Stage 3 SVD, in a patient on dialysis.[14]

The early results of this study with the INSPIRIS RESILIA valve demonstrate encouraging clinical results, with excellent 1-year survival and a haemodynamic performance comparable to that of the Carpentier-Edwards PERIMOUNT Magna Ease valve. Long-term studies are needed to evaluate the durability of the INSPIRIS RESILIA valve.[14]

Sex does not appear to influence left ventricular hypertrophy after aortic valve replacement

Benedikt P. Presented at ÖGHTG meeting, 29 May 2024, Salzburg, Austria.[15]

Some evidence suggests that left ventricular (LV) hypertrophy regresses more quickly in males than females after AVR. At the ÖGHTG meeting, Dr Benedikt from Johannes Keppler University, Linz, Austria presented an analysis of LV regression in patients who had undergone AVR with a RESILIA tissue valve at this institution and were included in the IMPACT prospective multicentre registry.[15]

Three-year follow-up data were available for 32 patients, 14 females and 18 males. Mean gradients at 3 years were comparable between males and females. Likewise, the reduction in the thickness of both the interventricular septum and the LV posterior wall were similar for males and females, suggesting that rate of LV hypertrophy regression was not faster in males in this study. A wider analysis of all patients in the IMPACT registry is planned.[15]

Bicuspid *versus* tricuspid morphology: No difference in outcomes in the IMPACT and INDURE registries

Damian I. Presented at ÖGHTG meeting, 29 May 2024, Salzburg, Austria.[16]

Bicuspid morphology is more prevalent in younger patients undergoing AVR; however, data on performance and outcomes following AVR are scarce. At the ÖGHTG meeting, Dr Damian from Johannes Keppler University, Linz, Austria presented 2-year follow-up results from a subgroup analysis of patients under 60 years of age from the IMPACT and INDURE registries assessing outcomes for the INSPIRIS RESILIA aortic valve.[16]

Of a total of 641 patients, 455 had a BAV and 186 had a tricuspid aortic valve (TAV). Patients with BAV were younger than patients with TAV (mean age: 53.2 ± 7.2 years *versus* 55.6 ± 4.9 years, p<0.001) and had a larger LV outflow tract (mean: 23.5 ± 3.8 mm *versus* 22.3 ± 3.2 mm, p<0.001). Concomitant supracoronary aortic graft procedures were more common in patients with BAV (22% *versus* 8.6%, p<0.001), and mean valve size was larger (24.7 ± 2.3 mm *versus* 24.0 ± 2.3 mm, p=0.001) compared with TAV.[16]

Overall, at 2 years, freedom from all-cause mortality was 96.0% (95% CI 94.2–97.8), freedom from prosthetic valve endocarditis was 97.8% (96.5–99.2), and freedom from Stage 3 SVD was 100%. No differences in freedom from mortality or adverse event rates were seen in patients with BAV compared with TAV.[16]

This merged analysis of two large international registries of younger patients confirmed the excellent outcomes for SAVR, with lower than predicted mortality, a satisfactory rate of endocarditis and no SVD. No differences in mortality or safety outcomes were observed in patients with BAV compared with TAV.[16]

COMMENCE trial at AATS: RESILIA tissue offers similar outcomes for patients with mixed aortic valve disease and pure aortic stenosis at 5-year follow-up

Thourani VH *et al*. Abstract 16, presented at the AATS 104th Annual Meeting, 27–30 April 2024, Toronto, ON, Canada.[17]

MAVD, the combination of aortic stenosis (AS) and aortic regurgitation (AR), is associated with worse patient outcomes than for those with pure AS. Better understanding of clinical and haemodynamic outcomes, as well as the optimal timing for intervention, in patients with MAVD is needed.

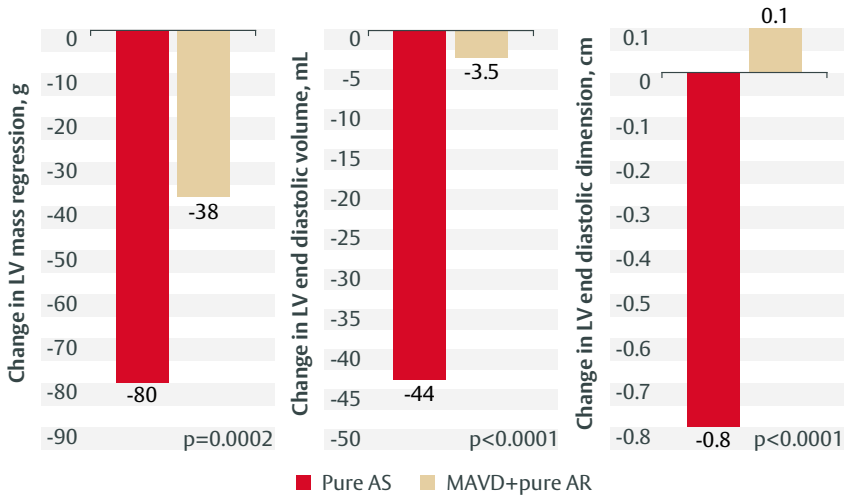
At the AATS Annual Meeting in April, Professor Vinod Thourani from the Piedmont Heart Institute in Atlanta, GA, USA presented a subanalysis from the COMMENCE trial comparing the 5-year safety and haemodynamic outcomes of patients with MAVR or pure AR (n=135) with those with pure AS (n=323).

The COMMENCE aortic trial is a prospective, multicentre, single-arm investigational device exemption study of SAVR with a RESILIA tissue valve.

Clinical outcomes at 5-year follow-up

Severity of AS at baseline in the MAVD/AR cohort had no effect on survival probability up to 5 years post implant. Baseline patient characteristics and haemodynamics were significantly different between groups, so a balancing score was calculated and used for adjusted analyses. No SVD or non-structural valve dysfunction was observed in either group. Adjusted Kaplan–Meier estimates (± standard error [SE]) were similar between patients with MAVD/AR and pure AS for all-cause mortality (88.3 ± 3.7% *vs* 87.4 ± 2.1%, p=0.67) and reoperation (97.9 ± 1.6% *vs* 99.0 ± 0.7%, p=0.43). Mean gradient and EOA were clinically stable over 5 years' follow-up and were similar between the two adjusted patient groups.

Compared with patients with pure AS, those with MAVD or pure AR demonstrated significantly greater left ventricular reverse remodelling



AR: aortic regurgitation; AS: aortic stenosis; LV: left ventricular; MAVD: mixed aortic valve disease.

- AVR with a RESILIA tissue valve demonstrated comparable 5-year safety outcomes between patients with pure AR or MAVD and those with pure AS
- Freedom from all-cause mortality for patients with pure AR was 96.3% at 5 years
- The significant LV reverse remodelling found in the pure AR or MAVD group emphasises a need for early treatment in this subgroup of patients, before irreversible changes occur

COMMENCE trial: Published 5-year data show excellent outcomes for RESILIA tissue valve in patients with bicuspid aortic valves

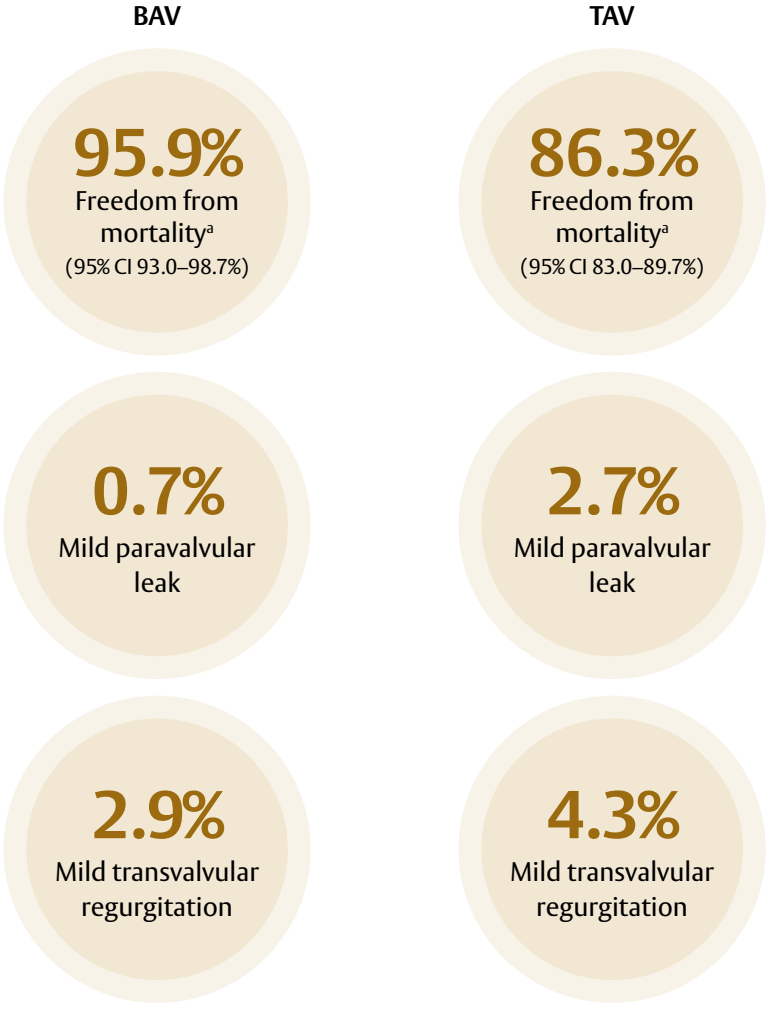
Bavaria JE *et al*. *Ann Thorac Surg*. 2024; **118:** 173–9.[18]

People with BAV are at increased risk of aortic valve disease, and present earlier than those with TAV, resulting in intervention at a younger age. Therefore, prosthetic valve durability is a concern in this patient subgroup. A subanalysis of the COMMENCE aortic trial compared safety and haemodynamic outcomes between patients with BAV (n=214) and TAV (n=458) after AVR. Here, we summarise the 5-year data, now published in *The Annals of Thoracic Surgery*.

Patients with BAV were, on average, more than a decade younger than those with TAV (mean ± standard deviation [SD]: 59.8 ± 12.4 years *vs* 70.2 ± 9.5 years, p<0.001) and had lower risk scores (EuroSCORE II: 1.8 ± 1.7% *vs* 2.7 ± 2.9%, p<0.001; STS PROM score: 1.2 ± 1.0% *vs* 2.3 ± 2.0%, p<0.001). Patients with BAV tended to be implanted with larger valve sizes than those with TAV (p<0.001), consistent with BAV commonly featuring aortic root and annular dilation.

Clinical outcomes at 5-year follow-up

No SVD was observed in either group at 5 years. Haemodynamics were clinically stable up to 5 years and comparable between the BAV and TAV cohorts (5-year mean gradient [mean ± SD]: BAV 11.5 ± 6.4 mmHg, TAV 11.6 ± 5.8 mmHg; EOA: BAV 1.66 ± 0.56 cm^2, TAV 1.53 ± 0.52 cm^2). Model-estimated rates of change in mean gradient and EOA remained similar after adjusting for age, body surface area and valve size.



[a]p<0.001 with a log-rank test. BAV: bicuspid aortic valve; CI: confidence interval; TAV: tricuspid aortic valve.

AVR with a RESILIA tissue valve showed excellent clinical and haemodynamic outcomes up to 5 years in patients with BAV, despite being a much younger cohort than the TAV cohort. The zero rate of SVD in either cohort is promising for the durability of RESILIA tissue valves in younger patients.

Perspective of a cardiac surgeon on lifetime management of patients using the INSPIRIS RESILIA and MITRIS RESILIA valves[a]

Dr Patrick Klein is a cardiac surgeon at the Amsterdam University Medical Centre, the Netherlands.

Q. The 2021 ESC/EACTS Guidelines for the management of valvular heart disease use patient age and surgical risk to guide the decision between SAVR and TAVI. If you could decide yourself, what revisions to these recommendations would you like to see in the 2025 guidelines?

A. I would like to see more precise recommendations for patients with BAV. The 2021 guidelines say that SAVR is the more favourable treatment option for these patients, but I think that the suitability criteria should be expanded to incorporate, for example, calcium distribution in bicuspid morphology.

Life expectancy is very important, so I think that the 2025 guidelines need to empower the Heart Team to guide the treatment decision, by integrating the latest data on both long-term outcomes after SAVR and TAVI, and individual/national life expectancy.

Q. Talking about the surgical approach, does your decision making for patients with aortic valve disease differ to that for mitral valve disease, and if so, how?

A. Yes, it does, because they are different diseases with different outcomes. Repair, where possible, is my focus for mitral valve disease. And if we need to replace the valve, then we need to consider durability.

Durability data are lacking for the MITRIS RESILIA valve, but its durability is likely to be less than that for the INSPIRIS RESILIA valve because of the reduced durability of bioprotheses in the mitral position compared with the aortic position.

Patients in the Netherlands undergoing AVR are, on average, around 72 years old, with a life expectancy of about 15 years, which must be considered when choosing a prosthetic valve. As such, I work with age thresholds of 50–55 years for an aortic bioprosthesis and 65 years for a mitral one.

Q. One of the open discussions is about antithrombotic strategies following valve replacement. Have the guidelines around novel oral anticoagulants affected your recommendations for the type of prosthesis (tissue or mechanical) your patients receive?

A. No, because I rarely implant a mechanical valve. For patients under 50 years old without an indication for a biological valve, I think that the Ross procedure is the preferred approach. For older patients, I recommend a biological valve, and I give them aspirin only, unless the patient has atrial fibrillation or another indication for warfarin.

Q. How are RESILIA tissue valves impacting your recommendations for the lifetime management of your patients?

A. The preclinical data for RESILIA tissue valves are strong on anticalcification, and the COMMENCE trial data have shown low SVD rates up to 7 years. Based on these data, I have started to implant biological valves at a younger age. I performed my first INSPIRIS RESILIA valve implantation in 2018. Before then, I would have hesitated to implant a biological valve in a patient younger than 60 years old, but now I've dropped the age threshold to 50 years.

[a]Expert opinion, advice and all other information expressed represent contributors' view and not necessarily those of Edwards Lifesciences

Q. How do you approach the shared decision-making process?

A. I always discuss lifetime management with my patients – it's a Class I recommendation to consider their well-informed choice.[13] I tell them that while the surgery takes just a few hours and they should be home in a week, they have to live with the prosthesis for 10–15 years, so they need to be well-informed.

I explain the differences between mechanical and biological valves, including the risk of bleeding, taking into account the patient's age and comorbidities. I also discuss the potential need for a second intervention with biological valves, and I explain the precautions I take to ensure that they can have a future valve-in-valve procedure. These include not implanting a very small valve in younger patients. I use a minimum of a 23 mm bioprosthesis – preferably larger – to allow for a valve-in-valve implant, and I have a low threshold for root enlargements to accommodate a bigger valve.

Q. What does the future hold for patients with valvular heart disease?

A. I think the future holds more tailored, less invasive treatment for patients, with their lifetime management considered by using a valve with good, predictable durability.

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No clinical data are available that evaluate the long-term impact of RESILIA tissue in patients. Additional clinical data for up to 10 years of follow-up are being collected to monitor the long-term safety and performance of RESILIA tissue.

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