Inspire

Your latest news on RESILIA tissue

Newsletter #2 – September 2022

Life^{R}

Life to the power of RESILIA

A promise of freedom. That's the power of RESILIA tissue.

Edwards

In this issue

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On the circuit

RESILIA tissue data presented on both sides of the Atlantic

At the Society for Cardiothoracic Surgery (SCTS) annual meeting in Belfast, UK in early May, Bart Meuris (University Hospitals Leuven, Belgium) summarised the 1-year outcomes from the INDURE registry. Between 2018 and 2021, 435 patients under 60 years old were enrolled in the registry. Find out the latest on page 2.

Over in Boston, MA, US, Joseph Bavaria (Hospital of the University of Pennsylvania, Philadelphia, PA, US) reported exciting results at the Annual Meeting of the American Association for Thoracic Surgery (AATS) in mid-May. In a sub-analysis of COMMENCE trial data, Dr Bavaria and colleagues investigated outcomes after surgical aortic valve replacement (SAVR) with a bioprosthesis containing RESILIA tissue in patients with bicuspid aortic valves (BAV). Turn to pages 3 and 4 to read a summary of the findings and Dr Bavaria's views on their significance.

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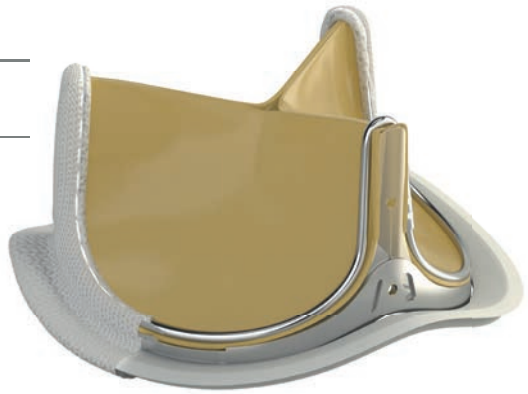
Hot off the press

Ricci A *et al*. *Surg Technol Int*. 2022; **40**: sti40/1496



A bioprosthesis resistant to calcification is the holy grail of substitutive heart surgery, according to Alessandro Ricci and colleagues at the European Hospital in Rome, Italy. In a recent article in *Surgical Technology International*, they review the evolution of bioprostheses and new anticalcification technologies, before moving on to discuss their experience with INSPIRIS RESILIA valve.[1] In 2 years, they've had **no cases of structural valve deterioration (SVD), endocarditis, detachment or periprocedural complications** with this valve. While they acknowledge that longer-term experience is needed, they describe results so far as encouraging for INSPIRIS RESILIA valve.

SAVR outcomes in patients under 60 years old

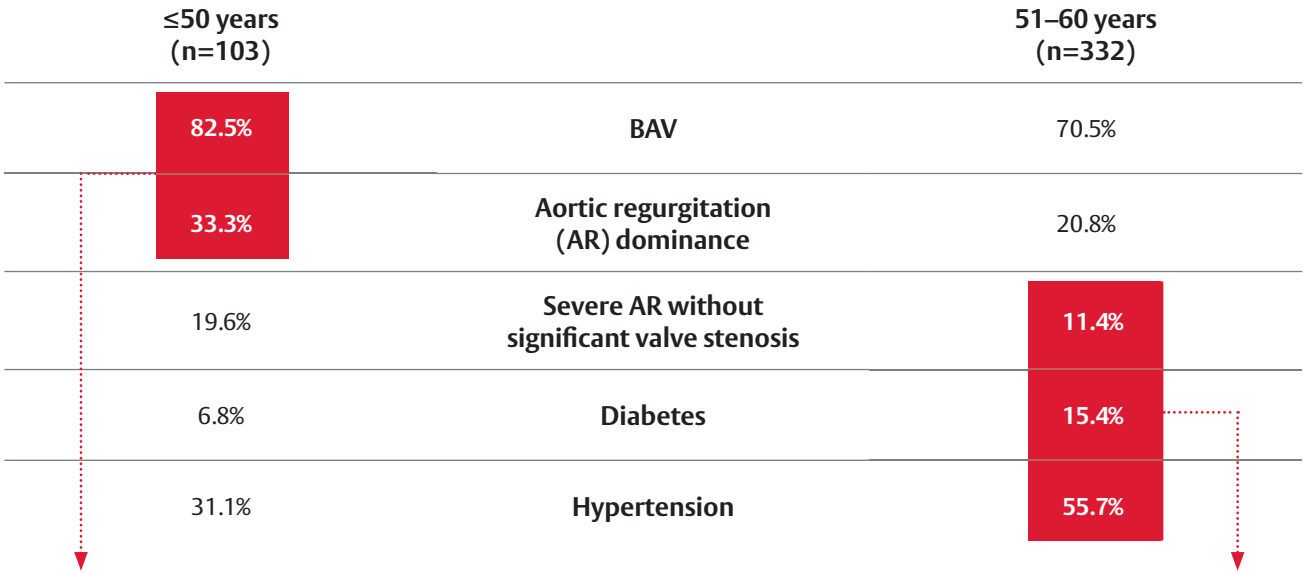
INDURE is a prospective, multicentre registry – with 5-year core-lab adjudicated follow-up – to assess the outcomes of SAVR with INSPIRIS RESILIA valve in patients younger than 60 years old. At the SCTS meeting in May 2022, Bart Meuris (University Hospitals Leuven, Belgium) presented 1-year data on the 435 patients enrolled at 21 sites in Europe and Canada.[2]

Key patient demographics

- Mean age: 53 years
- Female: 22.5%
- EuroSCORE II: 1.6±1.9%
- NYHA class III–IV: 25.9%

At baseline:

Comparing younger with older patients revealed some significant differences:



Younger (≤50 years) patients more likely to have AR at baseline or a BAV

Older patients (51–60 years) more likely to have aortic stenosis, diabetes or hypertension

Over half (59%) of patients underwent isolated SAVR; the same proportion received a 21- or 23-mm valve. Just over a quarter of procedures (27%) were minimally invasive. Patients stayed a median of 29.5 hours on the intensive care unit, with an overall hospital stay of 7 days. Thirty-day mortality was 0.7%.

At 1 year (n=196):

0%	1.1%	4.1%	12.7%	1.8 cm^2
Stage 3 SVD*	Endocarditis	All-cause mortality	Mean pressure gradient	Effective orifice area

Overall, preliminary 1-year follow-up outcomes from the INDURE registry confirm satisfactory safety and performance of INSPIRIS RESILIA valve in patients under 60 years old. SVD typically occurs more quickly in younger patients than in older ones,[3] so these early results for INSPIRIS RESILIA valve in this young population are promising. Longer-term follow-up is ongoing.

*Stage 3 SVD defined according to Salaun E *et al.* 2018[4]

Congress deep dive

Dr Joseph Bavaria on the COMMENCE bicuspid aortic valve sub-analysis

Joseph Bavaria (Hospital of the University of Pennsylvania, Philadelphia, PA, US) presented the results of a sub-analysis of 5-year COMMENCE aortic trial data, focusing on patients with BAV, at the AATS annual meeting in Boston, MA, US.[5] We spoke with him to discuss the importance of the results.

Q. What are the overall objectives of the COMMENCE aortic trial? Why is it important to evaluate outcomes in patients with BAV?

A. The COMMENCE aortic trial is a US FDA Investigational Device Exemption study, evaluating the safety and effectiveness of SAVR using a bioprosthesis with RESILIA tissue. As one of the more recent SAVR trials done in the transcatheter aortic valve implantation (TAVI) era, the COMMENCE trial has a younger patient population than previous SAVR trials, because older patients now receive TAVI instead. As a result, more than 30% (n=214) of our analysis cohort had BAV. BAV is common but excluded from most TAVI trials because outcomes tend to be poorer than for patients with tricuspid aortic valves (TAV). Placing a TAVI valve in a BAV can be challenging because of high calcium levels within the valve, which also often has a non-circular, non-planar annulus, leading to more paravalvular leak (PVL). Hence, we needed high quality data on BAV SAVR to demonstrate the benefits of this option for this important subgroup. We also specifically looked at patients aged ≤65 years, to tie in with the American College of Cardiology/ American Heart Association guidelines, and compared against those aged 66–75 years. This trial is robust, prospective, adjudicated by an independent clinical events committee and analysed by an independent echo core laboratory, so we can be confident in the results.

Q. Can you describe a typical patient with BAV in this trial? How did they vary from patients with TAV?

A. The average age in the BAV cohort was just over 59 years old – 10.5 years younger than patients with TAV. Patients with BAV had lower Society of Thoracic Surgeons risk scores than patients with TAV. They also had larger annuli so they received bioprostheses on average 1.1 mm bigger. Otherwise, the two cohorts were similar: mostly male (~70%), with aortic stenosis (52%) or mixed aortic stenosis/insufficiency (40%).

Q. What do the 5-year outcomes mean for the use of RESILIA tissue in patients with BAV and younger patients in general?

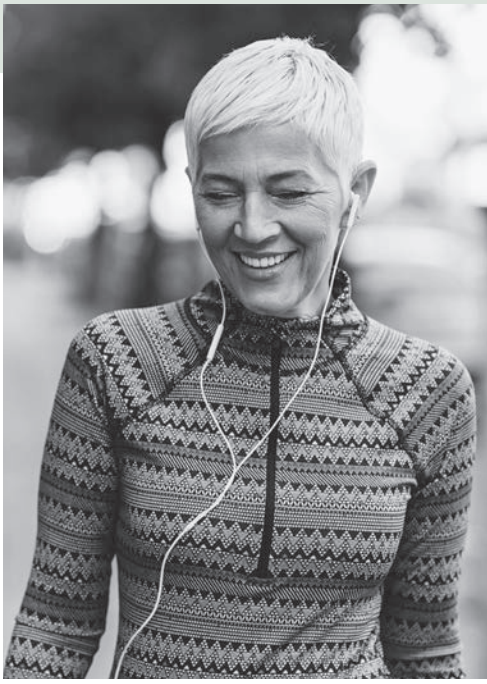
A. We saw no SVD over 5 years in the overall BAV cohort or in the ≤65 years subgroup – that's incredible. Central leak rate and mean gradient change over the study were negligible. As these are early markers for SVD, these results are really positive for RESILIA tissue in young patients. The PVL rate in the COMMENCE trial was around 10 times less than TAVI trial rates, and was actually lower in the ≤65 years BAV subgroup than in the 66–75 years subgroup.*

Q. What are the nextmajor milestones for the COMMENCE aortic trial and RESILIA tissue?

A. We are following a subset of COMMENCE patients out to 10 years – 7-year data are expected next year. Analysing how RESILIA tissue performs in patients with renal dysfunction could also be interesting. There's also a related trial – RESILIENCE – in which we are monitoring actual and subclinical calcification of RESILIA tissue in patients <65 years for 11 years, using echocardiography and computed tomography. We aim to find out what happens in the early stages of structural attrition before it starts affecting the patient.

*Difference in PVL rates between age subgroups was not analysed for significance because patient numbers were too small

Five-year outcomes following bicuspid aortic valve replacement with RESILIA tissue



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Bavaria JE *et al*. Presented at the 102nd Annual Meeting of the AATS, 2022

In a sub-analysis of 5-year data from the COMMENCE aortic trial, Dr Bavaria and colleagues sought to investigate safety and effectiveness outcomes in patients with BAV. Using models, they estimated changes in mean gradient, effective orifice area (EOA), PVL and central leak over 5 years postoperatively.[5]

Key 5-year outcomes in patients with BAV

Safety

95.9%	94.6%	100%	100%	100%
Freedom from mortality	Freedom from stroke	Freedom from valve thrombosis	Freedom from SVD*	Freedom from endocarditis

Haemodynamics

11.5 mmHg	1.66 cm^2
Mean gradient	EOA

Regurgitation

99%	97%
None/trivial PVL	None/trivial central leak

How did BAV outcomes compare with TAV outcomes?

Patients with BAV were **10 years younger**† with higher freedom from mortality‡ than patients with TAV, but there were no significant differences in morbidity or change in gradient or EOA over time.

In summary, SAVR with a RESILIA tissue bioprosthesis resulted in low major morbidity, mortality and regurgitation throughout 5 years in patients with BAV.

*SVD defined as dysfunction or deterioration involving the operated valve (exclusive of infection or thrombosis), as determined by reoperation, autopsy or clinical investigation

†10-year difference in mean age

‡BAV 95.9% *vs* TAV 86.3%, p=0.0004

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INSPIRIS RESILIA valve

A 1 billion cycle *in vitro* study

Sadri V *et al. JTCVS Open*. 2022; **9**: 59–69

Understanding the long-term performance and durability of bioprostheses new to the market can be difficult, but *in vitro* testing can help. Vahid Sadri and colleagues at Georgia Institute of Technology and Emory University, Atlanta, GA, US, simulated 25 years of use on INSPIRIS RESILIA valve using accelerated wear testing (AWT). The AWT machine moved saline solution through the valve so the leaflets opened and closed as they would in the body, but at an accelerated frequency.

They put three 21-mm valves and three 23-mm valves through 1 billion cycles, measuring their haemodynamic performance both before and afterwards. They then randomly selected one valve of each size for particle image velocimetry and leaflet kinematic testing.

INSPIRIS RESILIA valve demonstrated good durability and haemodynamic performance after the 1 billion cycles. In fact, the 1 billion-cycled valves showed similar haemodynamics ($p<0.05$), kinematics (21-mm: $p=0.028$; 23-mm: $p=0.047$) and velocity flow fields to those of a zero-cycled valve, and all structural components remained intact.

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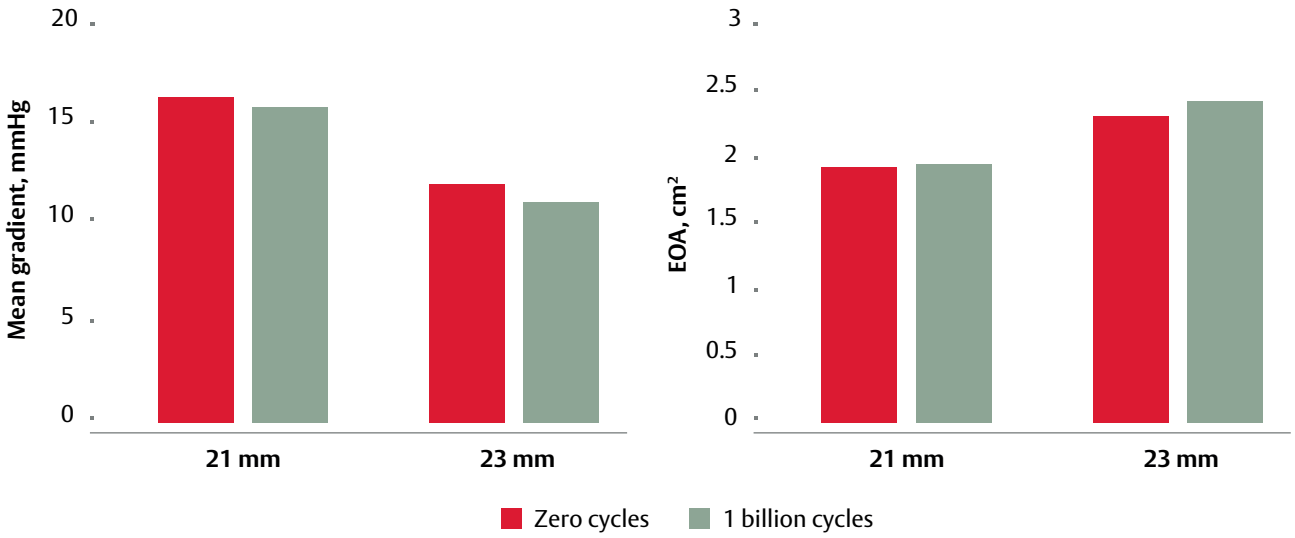
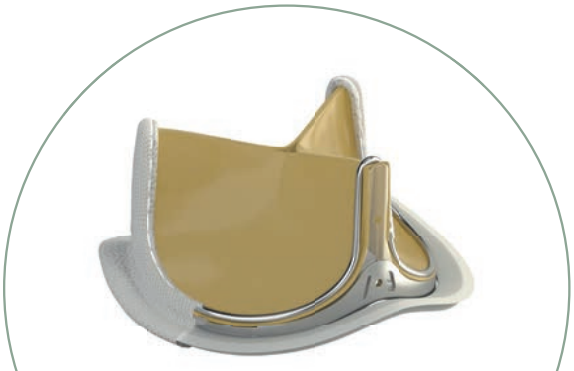
Mean gradient (left) and EOA (right) in INSPIRIS RESILIA valves, before and after 1 billion cycles of accelerated wear testing, by valve size



The International Organization for Standardization (ISO) mandates that biological heart valves are tested *in vitro* up to 200 million cycles, which is equivalent to 5 years *in vivo* use (ISO 5840-2:2015). In the study by Sadri *et al*., the valves still performed well after 1 billion cycles of simulated wear, five times longer than the standard requirement.



25 years of simulated wear *in vitro* demonstrated...

- Good durability
- Good haemodynamics
- Exceeded ISO requirements

Valves in practice: Hendrik Treede

Professor Hendrik Treede is Director of the Department of Cardiac Surgery at the Mid-German Heart Center, University Hospital of Mainz, Germany. He specialises in aortic and mitral valve surgery and often uses INSPIRIS RESILIA valve in his practice. We caught up with him to find out how he chooses the best valves for his patients.

Q. What are your main considerations when choosing which surgical valve to use in your patients?

A. First is the choice between mechanical and tissue valves. Most patients, including younger patients, now want a tissue valve. We tend to use mechanical valves on patients below the age of 50 only. We also consider life expectancy and anatomy when choosing between tissue valves.

Q. Please tell us about the use of INSPIRIS RESILIA valve in your practice.

A. It has quickly become our number one valve to implant. Our patient population has changed in recent years: high-risk, elderly patients are now treated with TAVI. Therefore, we focus on much younger patients, with a higher proportion of bicuspid valves. These are excellent candidates for INSPIRIS RESILIA valve because they have a long life expectancy and may be candidates for future valve in-valve procedures.

Q. What features of INSPIRIS RESILIA valve appeal to you?

A. It is easy to implant and ready to use straight from the shelf thanks to dry storage. Preclinical studies suggest enhanced durability,* and its VFit technology is intriguing for future valve-in-valve procedures. I also like that the valve's inner diameter is the same as the package claims. Size discrepancies for other valves can be immense.

Q. Would you recommend INSPIRIS RESILIA valve to other surgeons?

A. Definitely, I frequently do. We now 'compete' with TAVI so we need to deliver perfect quality for our patients. That means we consider not just acute survival after SAVR but long-term durability, as well as minimally invasive access routes to keep trauma as low as possible. INSPIRIS RESILIA valve fits well within these aims, offering all the good aspects of SAVR.

Q. What is your experience with other Edwards valves and technologies?

A. We've been using Carpentier-Edwards PERIMOUNT valves for decades. They are fantastic valves, supported by great long-term data. We continue to use the Magna Ease valve in patients with shorter life expectancies or with very large anatomies, as they wouldn't benefit so much from INSPIRIS RESILIA valve.

References:

1. Ricci A, Weltert LP, Lucertini G *et al.* Biological valves impervious to calcification: Is this Holy Grail a cup ready to drink? *Surg Technol Int.* 2022; **40**: sti40/1496.
2. Meuris B, Senage T, Senage T *et al.* Surgical aortic valve replacement outcomes in young patients under the age of 60. Society of Cardiothoracic Surgery Annual Meeting, 8–10 May 2022, Belfast, UK.
3. Head SJ, Çelik M, Kappetein AP. Mechanical versus bioprosthetic aortic valve replacement. *Eur Heart J.* 2017; **38**: 2183–91.
4. Salaun E, Clavel MA, Rodés-Cabau J *et al.* Bioprosthetic aortic valve durability in the era of transcatheter aortic valve implantation. *Heart.* 2018; **104**: 1323–32.
5. Bavaria J, Svensson LG, Pibarot P *et al.* Five-year outcomes following bicuspid aortic valve replacement with a novel tissue bioprosthesis. 102nd Annual Meeting of the American Association for Thoracic Surgery 14–17 May 2022, Boston, MA, US.

*No clinical data are available that evaluate the long-term impact of RESILIA tissue in patients.

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