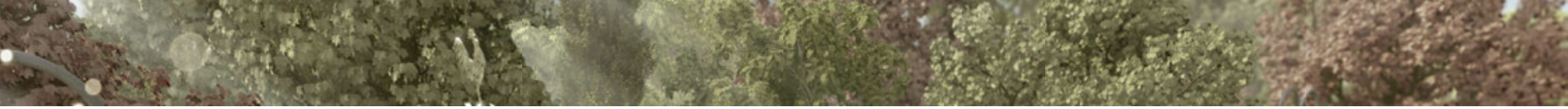
INSPIRIS RESILIA Aortic Valve Compendium

A class of resilient tissue valves

For use in replacement of native or prosthetic aortic heart valves.

Edwards



Your patients with aortic stenosis need an effective treatment that matches their needs[1–5]

Mortality increases rapidly in patients with aortic stenosis (AS) once symptoms appear.[1] On average, the probability of survival without treatment is around 60% at one year and 33% at three years.[2]

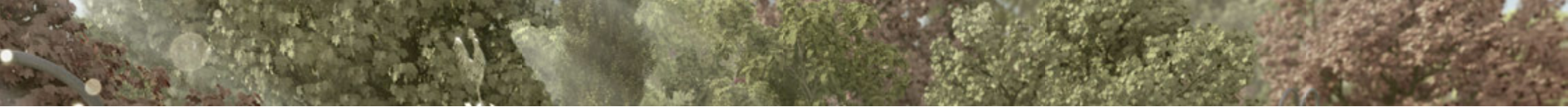
Patients with symptomatic, severe AS should be referred for intervention as soon as possible. Patients with less than severe AS should be continuously monitored and referred for intervention based on the type and severity of their symptoms.[3]

Which valve is right for your patient?
The 2017 ESC/EACTS guidelines give a Class IIa (level of evidence C) recommendation to the use of mechanical valves for patients aged <60 years, and tissue valves for patients >65 years.[3] However, the guidelines also acknowledge that the choice of valve replacement should be discussed with the informed patient taking many factors into consideration.[3]

Choosing between mechanical and tissue valves can feel like a compromise

Key factors to consider when choosing between a mechanical or tissue valve:

	Mechanical	Tissue
Need for lifelong anticoagulation[3]	Yes	No
Quality of life impact • More frequent physician visits[4] • Dietary restrictions[4] • Lifestyle and activity limitations[4] • Routine blood test monitoring[4,5] • Awareness of valve presence e.g. audible clicking sounds[6]	Greater impact on lifestyle	Lesser impact on lifestyle
Thrombosis/bleed risk[3,7]	Higher	Lower
Probability of re-operation due to valve durability[3,7]	Lower	Higher

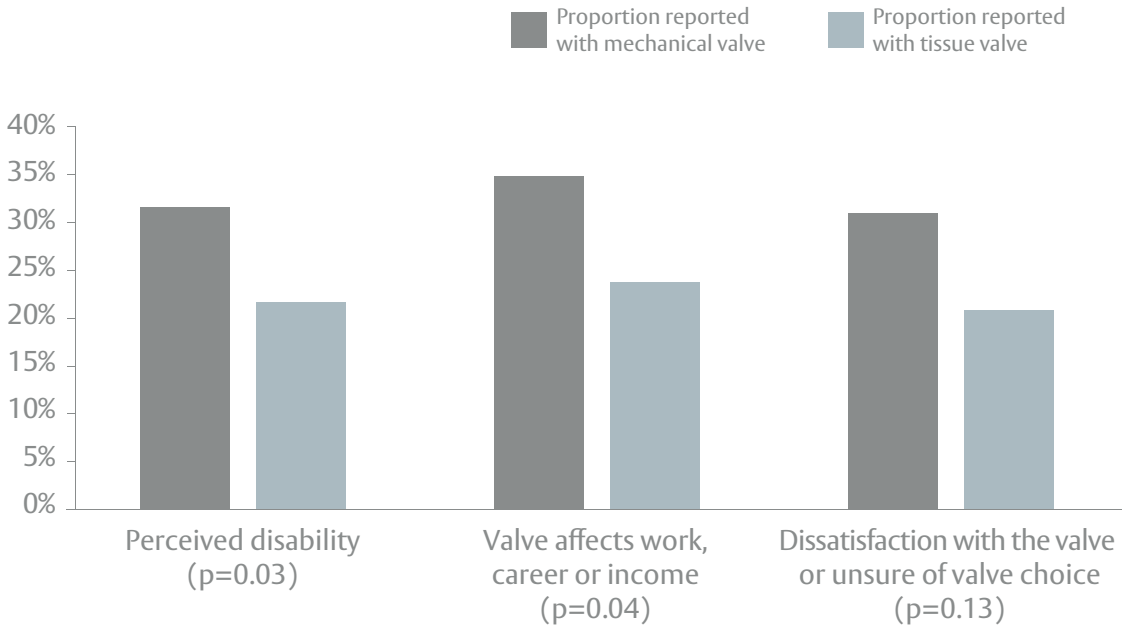


Quality of life impact – Living with a valve choice

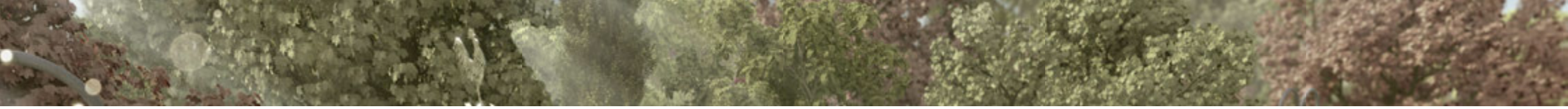
89% of patients agree that it is important to be involved in the selection of their valve[6] – a decision that is increasingly turning in favour of tissue valves as patients opt to continue living life without the compromises of anticoagulation.[8,9]

For patients who do receive a mechanical valve, their choice can have a major impact on their quality of life.*[10] Studies have shown a higher proportion of patients with mechanical valves reporting perceived disability, an effect on work, career or income, and dissatisfaction or unsureness toward their choice, compared with patients with tissue valves.*[10]

Patient perceived disability was seen to be ~10% higher with mechanical valves vs. tissue valves[10]



Adapted from Ruel *et al. Eur J Cardiothorac Surg.* 2005;27(3):425–433.[10]



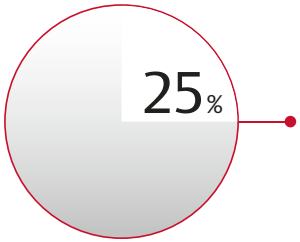
Thromboembolic and bleeding risk associated with anticoagulation therapy

Proper management of patient INR levels is essential for patients receiving anticoagulation therapy[3] to help avoid both an increased thromboembolic risk when dosages are too low, and an increased major bleeding risk when dosages are too high.[11]

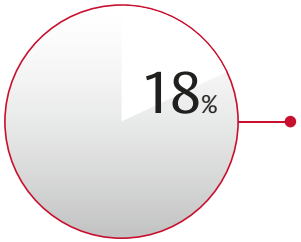
In order to help maintain target INR levels, guidelines recommend patient self-management when possible, provided the patient receives appropriate training.[3]

Increased frequency of INR monitoring can improve the chances of staying in range – 50% of those tested monthly were in target range vs. 85% of patients tested weekly[16]

Thromboembolic risk



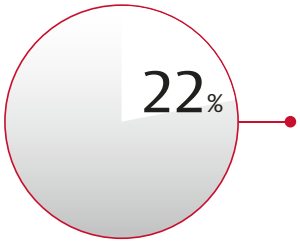
For a 25-year-old receiving a mechanical valve, the lifetime risk of a thromboembolic event is approximately 25%.[12]



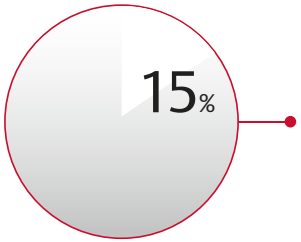
For a 45-year-old, the risk is approximately 18%.[12]

- The presence of another indication for long-term anticoagulation may require increased INR goals,[4] potentially making it more difficult to reach a desired INR. These include:[4]
  - Atrial fibrillation
  - Previous thromboembolism
  - Left ventricular dysfunction
  - Hypercoagulable conditions

Bleed risk

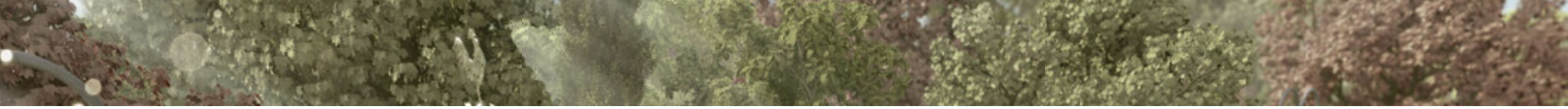


For a 25-year-old receiving a mechanical valve, the lifetime risk of bleeding is approximately 22%.[12]



For a 45-year-old, the risk is approximately 15%.[12]

- Anticoagulants require careful monitoring as they have been shown to increase bleeding risk through drug interactions.[13–15] For instance, this can occur with:
  - Antibiotics[13]
  - Non-steroidal anti-inflammatory drugs (NSAIDs)[14]
  - Antidepressants[15]



Managing reoperation risks

While probability of reoperation is significantly higher with tissue valves (the 15-year cumulative incidence of reoperation was higher with tissue valves than with mechanical valves: 12.1% [95% CI, 8.8%–15.4%] vs. 6.9% [95% CI, 4.2%–9.6%]; age range 50–69 years), survival rates and stroke associated with primary aortic valve replacement surgery are similar between valve types.[†17]

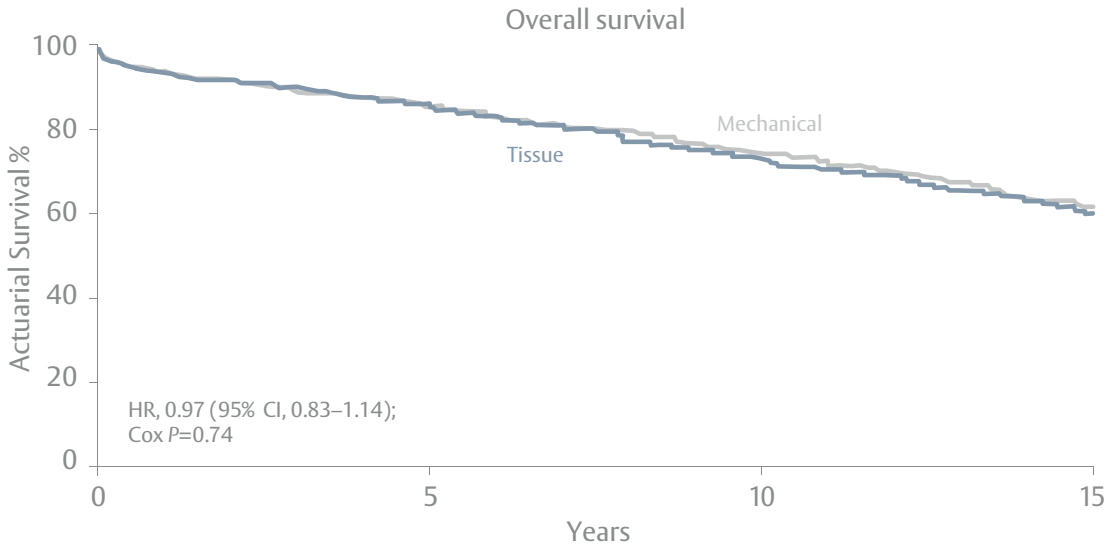
However, reoperation to replace a prosthetic valve can carry increased risk of operative mortality, morbidity, and thromboembolic events such as stroke, regardless of the valve type.[18]

Mechanical valves

- On average, mechanical valves are more durable than tissue valves[17]
- Present a higher risk of thromboembolism and anticoagulant-related bleeding[3]
- When dealing with thrombosis with mechanical valves, reoperation tends to be sudden, requiring emergency surgery which in itself is high risk[3]

Tissue valves

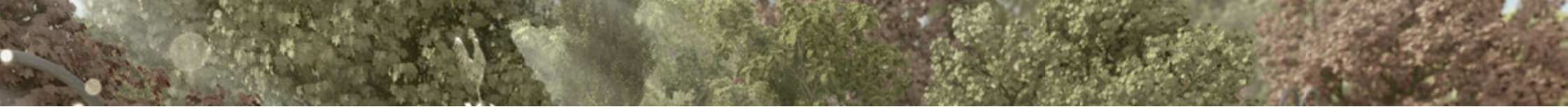
- Tissue valves are susceptible to structural valve deterioration and as such have greater reoperation rates in general[17]
- The option of valve-in-valve (ViV) procedures can make it possible for some patients to avoid reoperation via open heart surgery[19]



Adapted from Chiang *et al.*, *JAMA*. 2014;312:1323–1329.[†17]

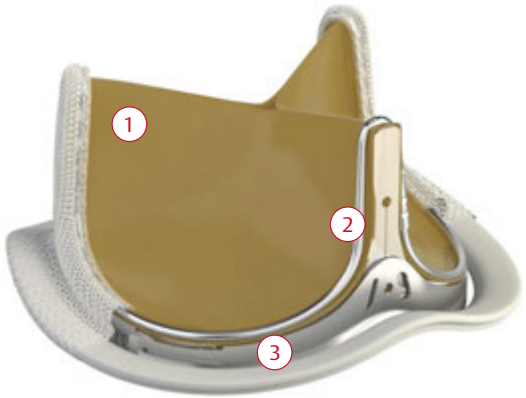
It is crucial to plan for the long-term impact of a prosthetic valve, especially in younger patients, and particularly in regards to key considerations such as avoiding future coronary occlusion and suboptimal haemodynamics, and the risk of reoperation due to structural valve deterioration.

Deciding between a mechanical or tissue valve requires an analysis of multiple factors, in particular, measuring bleed/thrombosis risks against structural valve deterioration[3]



Why the INSPIRIS RESILIA valve?

With an increasing general life expectancy,[20] patients need a valve prosthesis that will last longer. At the same time, patients are increasingly turning to tissue valves[8] in order to continue living life without the compromises of anticoagulation.[8,9,19]



1. RESILIA tissue
2. Trusted design and features of the PERIMOUNT valve platform
3. VFit technology

INSPIRIS RESILIA valve – the next generation of aortic tissue valve

1. RESILIA tissue

Edwards Lifesciences' integrity preservation technology transforms bovine pericardial tissue into RESILIA tissue, effectively eliminating free aldehydes, while protecting and preserving the tissue.[21]

The result is RESILIA tissue – the first tissue to deliver a combination of:

- Improved anti-calcification properties‡[22]
- Improved haemodynamic performance‡[22]
- Stored dry and ready to use§[21]

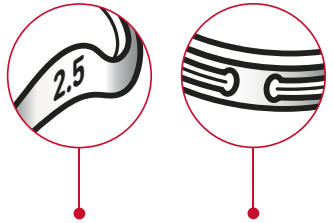
2. Trusted design and features

The INSPIRIS valve incorporates features of the trusted Carpentier-Edwards PERIMOUNT Magna Ease valve and is built on the proven design of the Carpentier-Edwards PERIMOUNT valve:

- Three independent leaflets matched for thickness and elasticity[21]
- Mathematically modelled, bioengineered design[21]
- Published clinical durability of over 20 years (PERIMOUNT valve)[22–25]
- Flexible, radiopaque cobalt chromium alloy wireframe[21]

3. VFit technology

VFit technology incorporates two novel features designed for potential future valve-in-valve (ViV) procedures:[21]



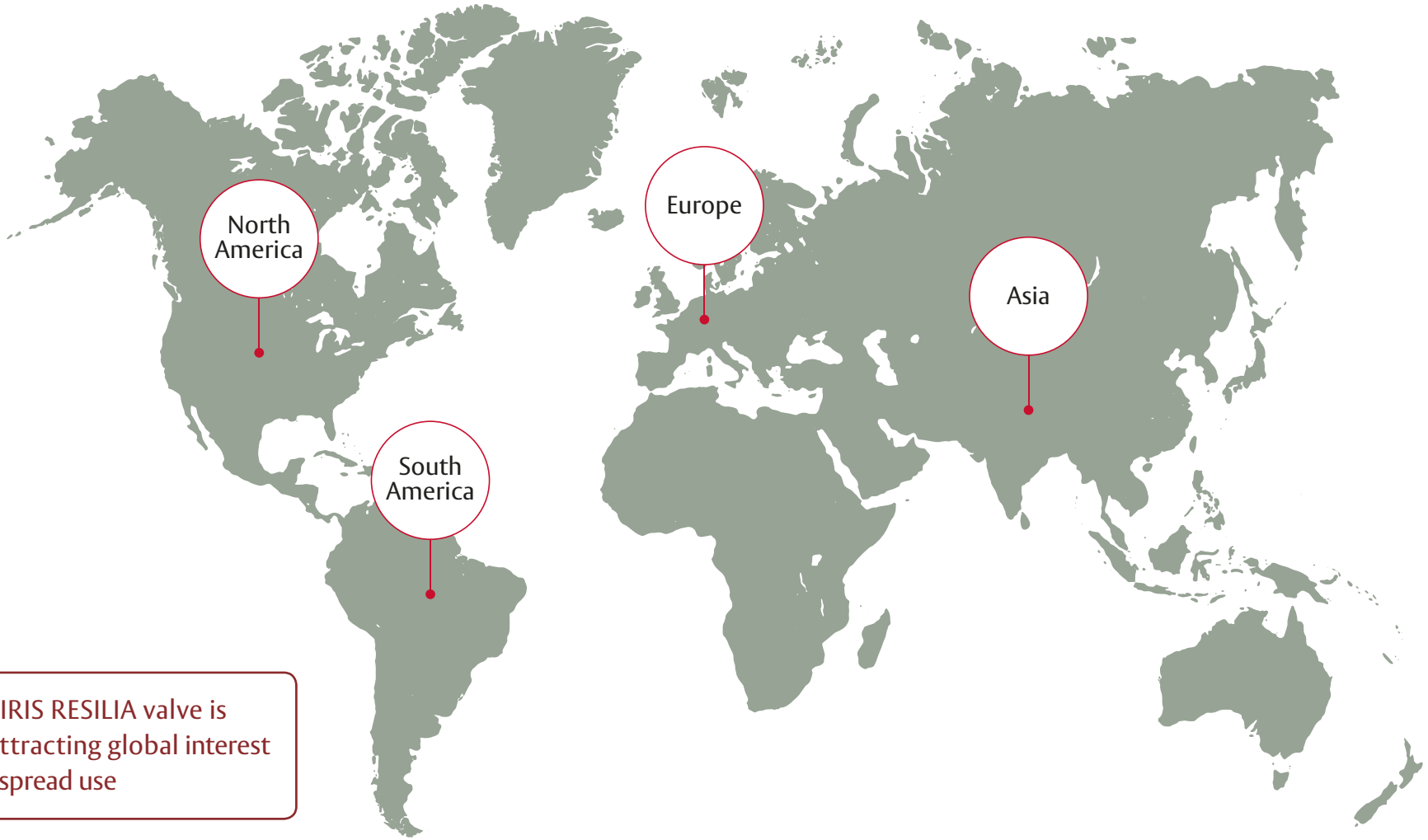
- Fluoroscopically visible size markers‖[21]
- Expansion zone‖[21]

Refer to device instructions for use 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.[21]

The INSPIRIS RESILIA valve has successfully been implanted in patients worldwide[26]

The INSPIRIS RESILIA valve, as of July 2019, has been successfully implanted in 20,000 patients worldwide.[26]

The INSPIRIS RESILIA valve has seen active use in:[26]

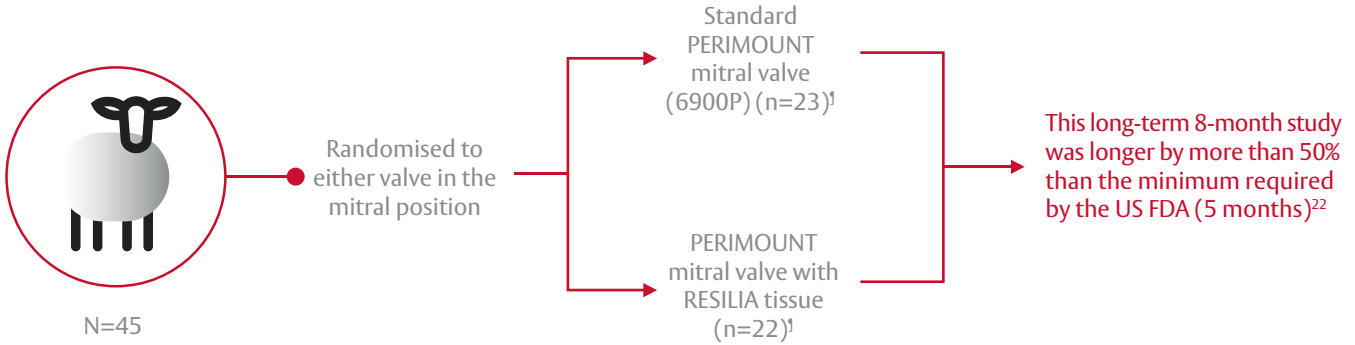


The INSPIRIS RESILIA valve is already attracting global interest and widespread use

Learnings from pre-clinical testing with RESILIA tissue

In a pre-clinical study using juvenile sheep in the mitral position (reflective of the accelerated calcification often seen in younger humans), RESILIA tissue in a PERIMOUNT valve demonstrated the following when compared to the standard PERIMOUNT valve:[22]

- 72% less calcification vs. control (p=0.002) (**Figures 1 and 2**)
- A significantly lower mean transvalvular gradient (PERIMOUNT valve with RESILIA tissue 3.9 mmHg vs. standard PERIMOUNT valve 5.5 mmHg; p=0.03) (**Figure 3**)
- Significantly lower occurrence of moderate-severe flow turbulence (PERIMOUNT valve with RESILIA tissue 6% vs. standard PERIMOUNT valve 64%; p=0.0008)



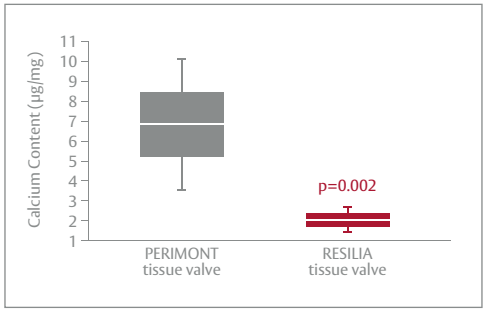


Figure 1
Final calcium content at the end of 8 months.

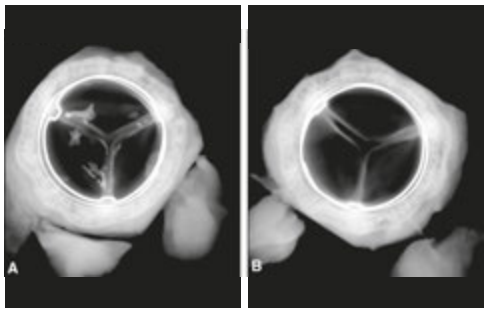


Figure 2
Radiographic analysis of explanted valves from the control group (A) and the test group (B). Calcium content was 72% lower with the RESILIA tissue valve, and mean gradient was significantly lower than in the control group.

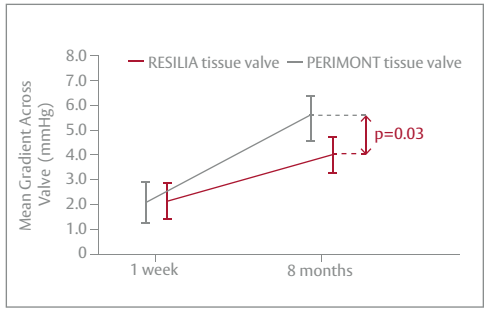
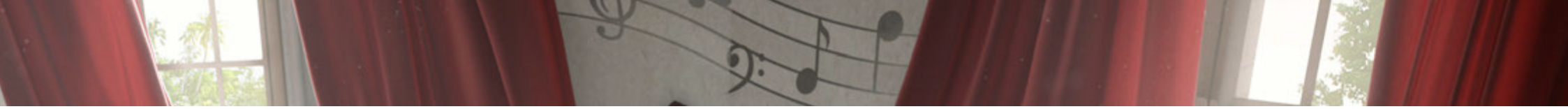


Figure 3
Change in mean gradient across the valve from 1 week to 8 months.

Significant improvements in haemodynamics, anti-calcification and transvalvular gradients, compared with the standard PERIMOUNT valve**[22]

Adapted from Flameng *et al. J Thorac Cardiovasc Surg*. 2015;149:340–345.[22]



The COMMENCE trial: evaluating RESILIA tissue performance over four years

COMMENCE is a prospective, multi-centre, single-arm study involving 689 patients (20.9% of whom were under 60 years of age).[27,28]

Patients underwent clinically indicated surgical AVR with a predecessor to the INSPIRIS RESILIA valve: the non-commercialised Edwards Pericardial Aortic Bioprosthesis with RESILIA tissue (Model 11000A).[27]

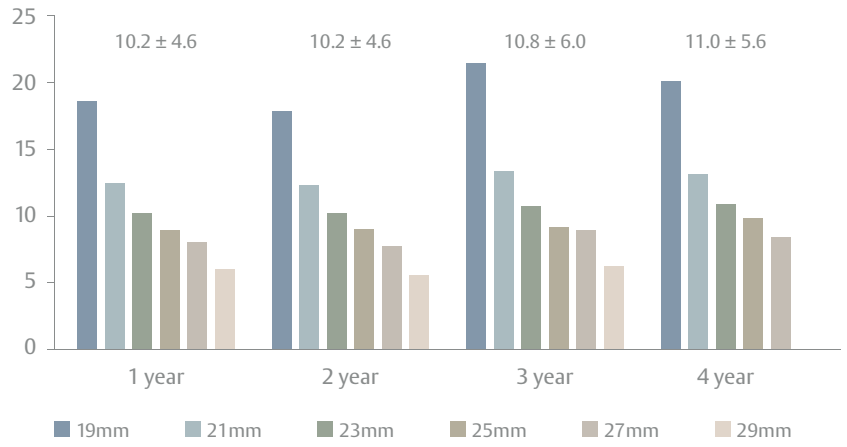
At 2-year (n=689) and 4-year (n=405) follow-ups,[27,29] the aortic valve with RESILIA tissue demonstrated:

- No cases of SVD with a favourable safety profile[27–29]
- Sustained haemodynamic performance[27–29]
- Low rates of paravalvular leaks (PVL)[27,29]
- An improvement in New York Heart Association (NYHA) class in 65.7% and 62.2% of patients, respectively[27,28]

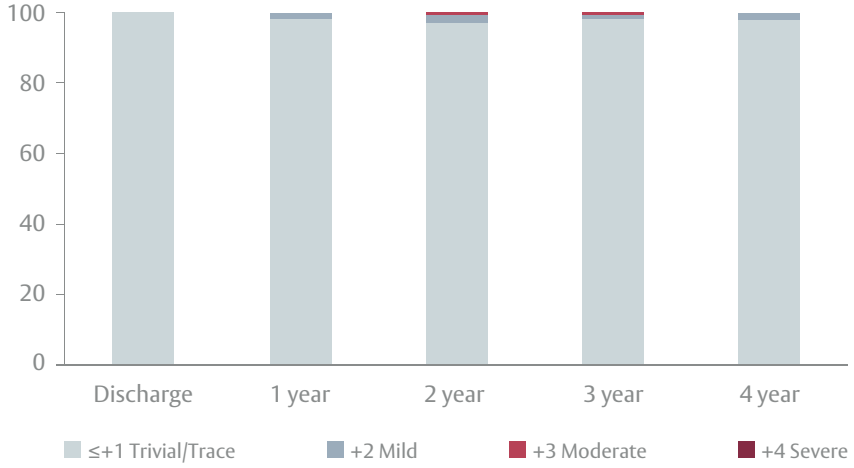
The COMMENCE trial is planned to have a 5-year follow-up.[30]

No cases of SVD seen over 4 years of follow up[27–29]

Mean gradient (mm Hg)[29]



PVL[29]



Adapted from Griffith *et al.* Oral presentation at the 99th Annual AATS Meeting, 2019.[29]

RESILIA European Feasibility study: the longest running evaluation of an INSPIRIS RESILIA tissue valve so far

The European Feasibility study is a prospective, multi-centre, single-arm study involving 133 patients (26% of whom were 60 years of age or under).[31]

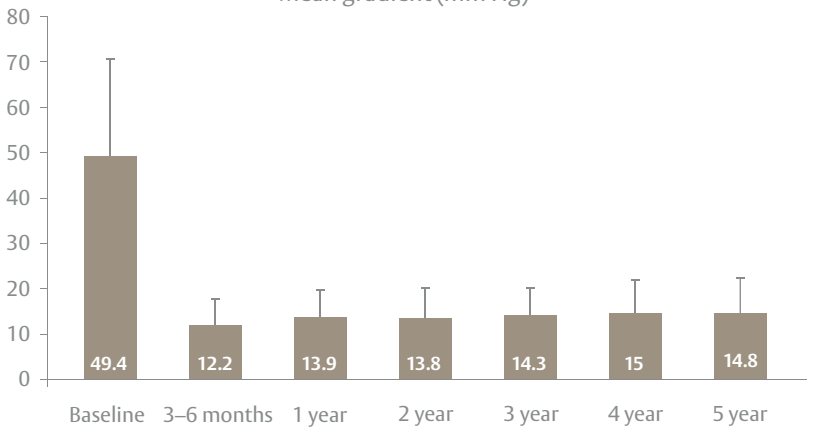
Patients received a predecessor to the INSPIRIS RESILIA valve, the non-commercialised Edwards Pericardial Aortic Bioprosthesis with RESILIA tissue (Model 11000A), and were followed over 5 years.[31,32]

At 4.2 ± 1.5 year mean follow-up (n=133),[31,32] the aortic valve with RESILIA tissue demonstrated:

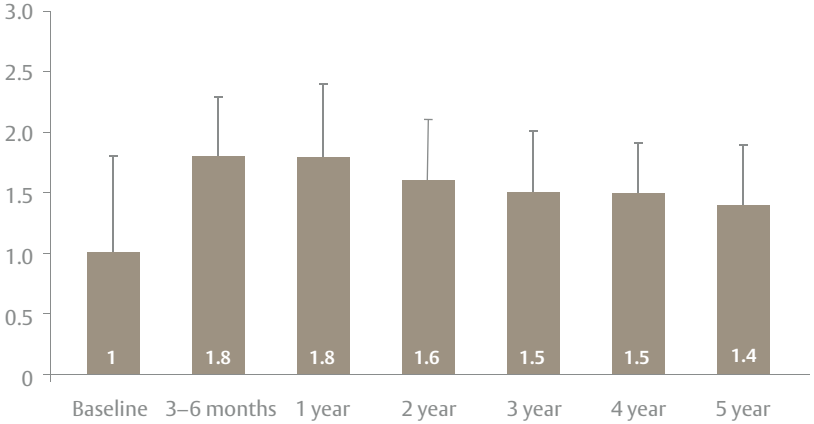
- No cases of SVD with an excellent safety profile[31,32]
- Sustained haemodynamic performance from baseline[32]
- Low rate of PVL[31,32]
- An improvement in NYHA class in 55% of patients[32]

The longest-running evaluation of RESILIA tissue demonstrated no cases of SVD[31,32]

Mean gradient (mm Hg)[32]



Effective Orifice Area (cm^2)[32]



Adapted from Bartus *et al.* Presented at the Heart Valve Society Annual Meeting, 2019.[32]

Looking onward: Investigating the INSPIRIS RESILIA valve in new trials

The RESILIENCE Trial

The RESILIENCE study is a prospective, multi-centre, observational evaluation of the durability of aortic bioprostheses/valves with RESILIA tissue in subjects under 65:[33]

- Up to 15 sites to be enrolled
- Up to 250 patients to be enrolled
- 5, 7, 9 and 11-year follow-up

The primary endpoint for the study will be the time to tissue valve failure due to structural valve deterioration or confirmed study valve-related death.[33]

Secondary endpoints will include the quantification of valve leaflet calcification, the haemodynamic performance of the valve, and evaluation for possible morphological/ haemodynamic valve deterioration.[33]

The RESILIENCE Trial is an Edwards sponsored trial. For more information, visit: https://clinicaltrials.gov/ct2/show/NCT03680040.[33]

INDURE

INSPIRIS RESILIA DURABILITY REGISTRY

The INDURE study is a prospective, open-label, real-world registry assessing the clinical outcomes of patients younger than 60 years who undergo aortic valve replacement with an INSPIRIS RESILIA valve:[34]

- Multiple European sites
- Minimum of 400 patients enrolled
- 5-year follow-up
- Time-related valve safety composite endpoint according to VARC-2

INDURE is an investigator initiated trial. For more information, visit: https://clinicaltrials.gov/ct2/show/NCT03666741.[34]

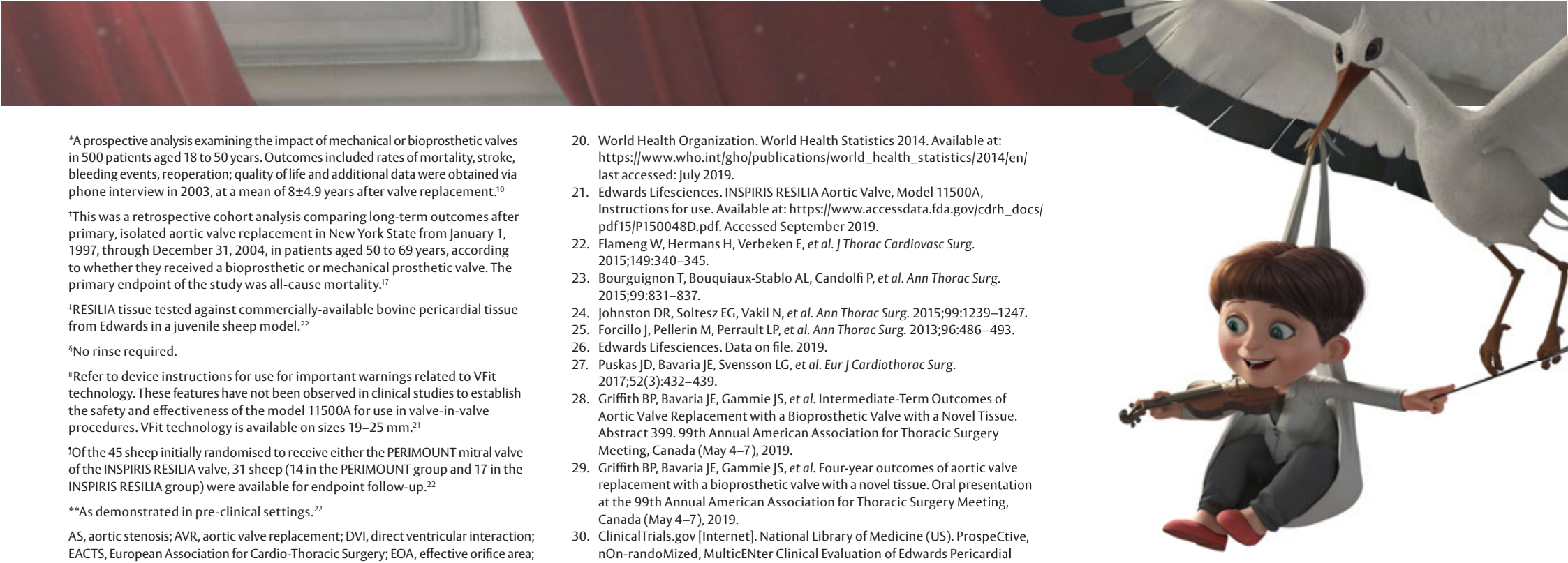
Edwards is dedicated to supporting the INSPIRIS RESILIA valve with the latest data

Help your patients with AVR feel reborn with the INSPIRIS RESILIA tissue valve

Across 4 years in the COMMENCE trial and 5 in the EU Feasibility study, RESILIA tissue has demonstrated:[27–29,31,32]

- No reported cases of SVD with a favourable safety profile
- Sustained haemodynamic performance
- Low rates of PVL
- Improvement in NYHA class in over half of patients

INSPIRIS RESILIA Aortic Valve The next generation of aortic tissue valves



*A prospective analysis examining the impact of mechanical or bioprosthetic valves in 500 patients aged 18 to 50 years. Outcomes included rates of mortality, stroke, bleeding events, reoperation; quality of life and additional data were obtained via phone interview in 2003, at a mean of 8±4.9 years after valve replacement.[10]

†This was a retrospective cohort analysis comparing long-term outcomes after primary, isolated aortic valve replacement in New York State from January 1, 1997, through December 31, 2004, in patients aged 50 to 69 years, according to whether they received a bioprosthetic or mechanical prosthetic valve. The primary endpoint of the study was all-cause mortality.[17]

‡RESILIA tissue tested against commercially-available bovine pericardial tissue from Edwards in a juvenile sheep model.[22]

§No rinse required.

‖Refer to device instructions for use 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.[21]

¶Of the 45 sheep initially randomised to receive either the PERIMOUNT mitral valve of the INSPIRIS RESILIA valve, 31 sheep (14 in the PERIMOUNT group and 17 in the INSPIRIS RESILIA group) were available for endpoint follow-up.[22]

**As demonstrated in pre-clinical settings.[22]

AS, aortic stenosis; AVR, aortic valve replacement; DVI, direct ventricular interaction; EACTS, European Association for Cardio-Thoracic Surgery; EOA, effective orifice area; ESC, European Society of Cardiology; INR, International Normalised Ratio; MPG, mean pressure gradient; NYHA, New York Heart Association; PVL, paravalvular leak; sAVR, surgical aortic valve replacement; SVD, structural valve deterioration; TAVI, transcatheter aortic valve implantation; VARC, Valve Academic Research Consortium; ViV, valve-in-valve.

1. Grimard B, Safford R, Burns E. *Am Fam Physician*. 2016;93(5):371–378.
2. Malaisrie SC, McDonald E, Kruse J, *et al. Ann Thorac Surg*. 2014;98:1564–1571.
3. Baumgartner H, Falk V, Bax JJ, *et al. Eur Heart J*. 2017;38:2739–2791.
4. Nishimura RA, Otto CM, Bonow RO, *et al. J Am Coll Cardiol*. 2017;70(2):252–289.
5. Nishimura RA, Otto CM, Bonow RO, *et al. J Thorac Cardiovasc Surg*. 2014;148(1):e1–e132.
6. Korteland NM, Top D, Borsboom GJ, *et al. Interact Cardiovasc Thorac Surg*. 2016;22(6):723–728.
7. Head SJ, MeÇelik M, Kappetein AP, *et al. Eur Heart J*. 2017;38(28):2183–2191.
8. Brown JM, O'Brien SM, Wu C, *et al. J Thorac Cardiovasc Surg*. 2009;137:82–90.
9. Schnittman SR, Adams DH, Itagaki S, *et al. J Thorac Cardiovasc Surg*. 2018;155:539–547.
10. Ruel M, Kulik A, Lam BK, *et al. Eur J Cardiothorac Surg*. 2005;27(3):425–433.
11. Kimmel SE, Chen Z, Price M, *et al. Arch Intern Med*. 2007;167(3):229–235.
12. Korteland NM, Etnel JRG, Arabkhani B, *et al. Eur Heart J*. 2017;38(45):3370–3377.
13. Baillargeon J, Holmes HM, Lin YL, *et al. Am J Med*. 2012;125(2):183–189.
14. Choi KH, Kim AJ, Son IJ, *et al. J Korean Med Sci*. 2010;25(3):337–341.
15. Schelleman H, Brensinger CM, Bilker WB, *et al. PLoS One*. 2011;6(6):e21447.
16. Heneghan C, Alonso-Coello P, Garcia-Alamino JM, *et al. Lancet*. 2006;367:404–411.
17. Chiang YP, Chikwe J, Moskowitz AJ *et al. JAMA*. 2014;312:1323–1329.
18. Kaneko T, Vassileva CM, Englum B, *et al. Ann Thorac Surg*. 2015;100(4):1298–1304.
19. Reul RM, Ramchandani MK, Reardon MJ. *Methodist Debakey Cardiovasc J*. 2017;13:132–141.
20. World Health Organization. World Health Statistics 2014. Available at: https://www.who.int/gho/publications/world_health_statistics/2014/en/ last accessed: July 2019.
21. Edwards Lifesciences. INSPIRIS RESILIA Aortic Valve, Model 11500A, Instructions for use. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150048D.pdf. Accessed September 2019.
22. Flameng W, Hermans H, Verbeken E, *et al. J Thorac Cardiovasc Surg*. 2015;149:340–345.
23. Bourguignon T, Bouquiaux-Stablo AL, Candolfi P, *et al. Ann Thorac Surg*. 2015;99:831–837.
24. Johnston DR, Soltesz EG, Vakil N, *et al. Ann Thorac Surg*. 2015;99:1239–1247.
25. Forcillo J, Pellerin M, Perrault LP, *et al. Ann Thorac Surg*. 2013;96:486–493.
26. Edwards Lifesciences. Data on file. 2019.
27. Puskas JD, Bavaria JE, Svensson LG, *et al. Eur J Cardiothorac Surg*. 2017;52(3):432–439.
28. Griffith BP, Bavaria JE, Gammie JS, *et al.* Intermediate-Term Outcomes of Aortic Valve Replacement with a Bioprosthetic Valve with a Novel Tissue. Abstract 399. 99th Annual American Association for Thoracic Surgery Meeting, Canada (May 4–7), 2019.
29. Griffith BP, Bavaria JE, Gammie JS, *et al.* Four-year outcomes of aortic valve replacement with a bioprosthetic valve with a novel tissue. Oral presentation at the 99th Annual American Association for Thoracic Surgery Meeting, Canada (May 4–7), 2019.
30. ClinicalTrials.gov [Internet]. National Library of Medicine (US). ProspeCtive, nOn-randoMized, MulticENter Clinical Evaluation of Edwards Pericardial Bioprostheses With a New Tissue Treatment Platform (COMMENCE). Available at: https://clinicaltrials.gov/ct2/show/NCT01757665; last accessed: July 2019.
31. Bartus K, Bilewska A, Bochenek M, *et al. Struct Heart*. 2019;3(S1):18.
32. Bartus K, Bilewska A, Bochenek M, et al. Five-year outcomes of aortic valve replacement using a bioprosthetic valve with the novel RESILIA tissue: final study results. Presented at the Heart Valve Society Annual Meeting, Spain (April 11–13), 2019.
33. ClinicalTrials.gov [Internet]. National Library of Medicine (US). RESILIENCE Trial: Evaluation of the Durability of Aortic Bioprostheses/Valves With RESILIA Tissue in Subjects Under 65 (RESILIENCE). Available at: https://clinicaltrials.gov/ct2/show/NCT03680040; last accessed: July 2019.
34. ClinicalTrials.gov [Internet]. National Library of Medicine (US). Inspiris Resilia Durability Registry (INDURE). Available at: https://clinicaltrials.gov/ct2/show/NCT03666741; last accessed: July 2019.

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