Biological Valves Impervious to Calcification: Is this Holy Grail a Cup Ready to Drink?

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ABSTRACT

An indefinitely lasting bioprosthesis that does not require anticoagulation treatment is the holy grail of substitutive heart surgery. However, this goal is not yet in sight with the present state of technology. Over the past few years, tremendous advances have been achieved regarding tissue anticalcification processes, hemodynamic performance and future-proofing by ensuring compatibility with transcatheter valve-in-valve procedures.

The Inspiris Resilia valve (Edwards Lifesciences, Irvine, CA) was designed to incorporate all of these enhancements. It is now leaving the experimental phase and is being tested in the real world.

We present here a comprehensive review of the evolution of biological prostheses, details of new anticalcification technologies, and early results of published studies as well as the experience at the European Hospital (Rome, Italy), the site of the first European implant and a leading center in various protocols. In our two years of experience with the Inspiris Resilia, there have been no cases of structural valve deterioration, endocarditis, detachment or periprocedural complication, and gradients seem to be superior to those with the previous generation of Edwards valves.

While longer-term experience is clearly needed, the results thus far are encouraging.

INTRODUCTION

A surgeon planning to implant a prosthetic heart valve faces a dilemma. Should they grant the patient a life reasonably free of intervention by implanting a mechanical device that forces the patient to permanently require oral anticoagulation, or should they grant the patient a reasonably long period of uncompromised quality of life regarding the burden of anticoagulation by using a biological valve prosthesis, knowing that this choice will inevitably require a reoperation?

This Hamletic doubt has been around since the 1970's, and is basically still unresolved.

Pyrolytic carbon technology, which lies at the core of the mechanical valve, has not advanced much over the last 40 years and the material is still not fully inert in the blood stream; thus, thrombus formation is still a risk if anticoagulation is not in place. On the other hand, more friendly approaches to anticoagulation such as new oral anticoagulation (NAO) have been deemed unsafe and thus discarded, thus relegating patients to be dependent on an old and still impractical medication strategy.

On the other hand, there have been great advances in the use of biological tissues, specifically regarding anticalcification treatment, based on capping of radicals, masking of antigens and preservation strategies to prolong their normal function and prevent early degeneration.

However, it seemed as if no technique made biological tissue fully compatible from immunological and chemical points of view. Therefore, the goal has been to slow the process of tissue calcification to prolong the time until a repeat procedure is needed.

Recently, with the introduction of transcatheter aortic valve implantation (TAVI) procedures to the clinical arena, the Valve-in-Valve concept has been popularized as a solution to the problem of structural valve deterioration, to exorcise the intrinsic fear of a second heart surgery.

In the real world, results regarding the durability of biological substitutes are inconsistent due to the many changes in design, implant technique, and labeling systems.

The market leader in biological valves (Edwards Lifesciences, Irvine, CA) has announced a breakthrough in anticalcification technology, which could potentially extend the duration of their biological valves by 30%. In many cases, this improved durability could exceed the life expectancy of the patient and could make younger patients eligible for a bioprosthesis as a destination therapy.

Because the bioprosthetic valve design has not been changed, and given the already well-known durability of the previous models of Edwards valves, this new option has gained a relatively fast and widespread acceptance by the community of surgeons worldwide.

The European Hospital in Rome was the theatre for the first Italian implant of this valve and has since been consistently proposing this type of bioprosthesis to relatively young patients who wish to avoid anticoagulation.

We present here an analysis of the published results and insight into our center's experience.

Technological Improvements – Dwarfs on the shoulders of giants

Important advances can be either revolutionary or evolutionary. The Inspiris Resilia (Edwards) definitely falls into the latter category and capitalizes on previous experience. Figure 1 shows a schematic of the generational evolution of Edwards valves. As depicted, the wireform that gives the valve its three-dimensional shape is made of a Chrome-Cobalt alloy, which hasn't changed since the original Perimount (Edwards) design, in terms of both design and material. The same material is also used at the base of the wireform to create a strong circular support for the sewing ring. The Inspiris features a basal ring very similar to the original version, with one improvement: the ring is discontinuous, and part of it overlaps in a sort of double layer, thereby allowing the ring to expand slightly if inflated from the inside with a balloon.

This small design modification was introduced with TAVI valve-in-valve procedures in mind, and looks promising.

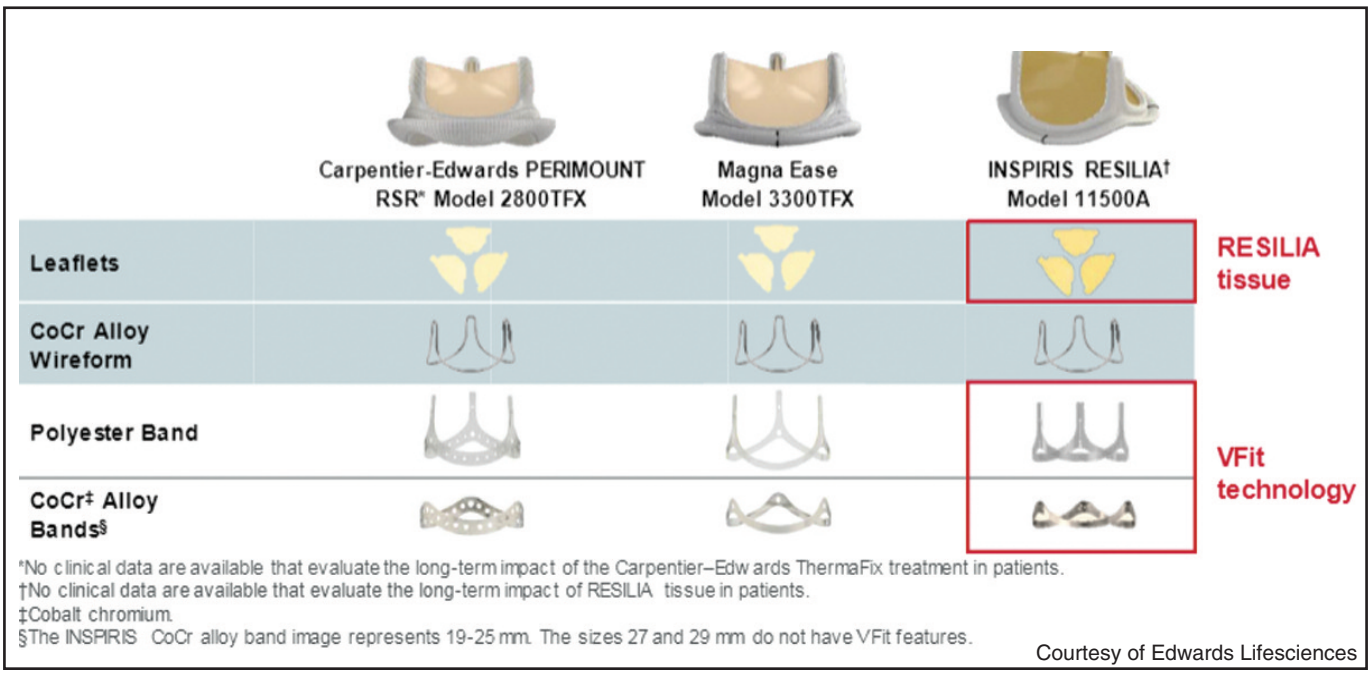

Figure 1. Comparison of the building blocks of Edwards biological valves (Edwards Lifesciences, Inc.).

The possibility of enlarging the ring of a degenerated bioprosthesis to insert a larger percutaneous bioprosthesis is certainly appealing.

This metallic structure is covered by a polyester band, with the same shape and characteristics as all Edwards bioprostheses on the market.

The biological tissue is sewed to the structure in the form of three leaflets. This biological tissue, so-called Resilia tissue, although similar in shape and thickness as in other applications, has been treated differently to be resistant to calcification and is the true novelty that is expected to increase valve durability.

Although it is marketed as a total novelty, Resilia tissue builds on a proven technology (ThermaFix, Edwards) that has been in use for about 20 years.

The ThermaFix process is a phospholipid extraction technique with glutaraldehyde stabilization, with consistent tissue preservation in terms of architecture. The Resilia process adds two more crucial steps, stable capping and glycerolization, which in turn allow sterilization and dry storage.

To understand why this process makes a difference requires an understanding of some chemical details. Collagen fibers, the core component of the biological leaflet, consist of amino acid sidechains. Glutaraldehyde fixation strengthens the tissue by creating crosslinks with the collagen matrix. However, in doing so, the process creates free aldehydes, which are a calcium-binding magnet in vivo. This Achilles' heel of the process has been known for a long time, but the solution has only recently been found: capping the free aldehydes with a small amine to form a base (technically an unstable Schiff base) which can be stabilized to form a covalent bond. The result is that the extremities of the free aldehydes, which were like fingers searching for calcium in the bloodstream, are now masked inside a stable "glove" that prevents bonding with calcium. To further cover the capped aldehydes, a coating of glycerol is added, which leads to both a further reduction in exposure to free aldehydes, and the possibility of conserving the valve in dry conditions, thereby avoiding the need for rinsing at the time of implantation.

This process took a full decade to implement, roughly from 2004 to 2016, and is depicted in Fig. 2.

As with any new technology, it wasn't until the presentation of the first in vivo evidence that the surgical community realized that something potentially very useful had been developed. This evidence consisted of the results of in vivo experimentation in sheep. The sheep is known to be an aggressive calcification model and is widely used in cardiovascular science to test this process.

In terms of statistical power, to ascertain a difference of at least 10% with a 10% standard deviation, an alfa error set to 0.05 and a power set to 80%, 16 subjects per group are usually needed. The study to test Resilia tissue enrolled 14 sheep in the control group (Perimount) while 17 sheep were implanted with Resilia valves in the mitral position, which is acceptable from a theoretical statistical point of view. The valves were explanted after six months and blindly assessed for the presence of calcification. The results exceeded all expectations. The reduction in calcification was 72%, as shown in Fig. 3, which also resulted in lower transvalvular gradients.

The in vivo human experience - From words to facts

The industry clearly perceived that something potentially useful and groundbreaking had been achieved, but the history of surgery is paved with stories of promising invention ending miserably. Therefore, caution is the mantra for every evolutionary step regarding medical devices.

From 2004 to 2010, Resilia tissue was evaluated in animals, first with small samples in small animals and then in large animals (as described above). In 2011, the first human European enrollment took place, in the form of a feasibility study in Poland that enrolled 133 all comer patients at two sites. A year later (2012), preliminary enrollment took place in the US, in a study with the

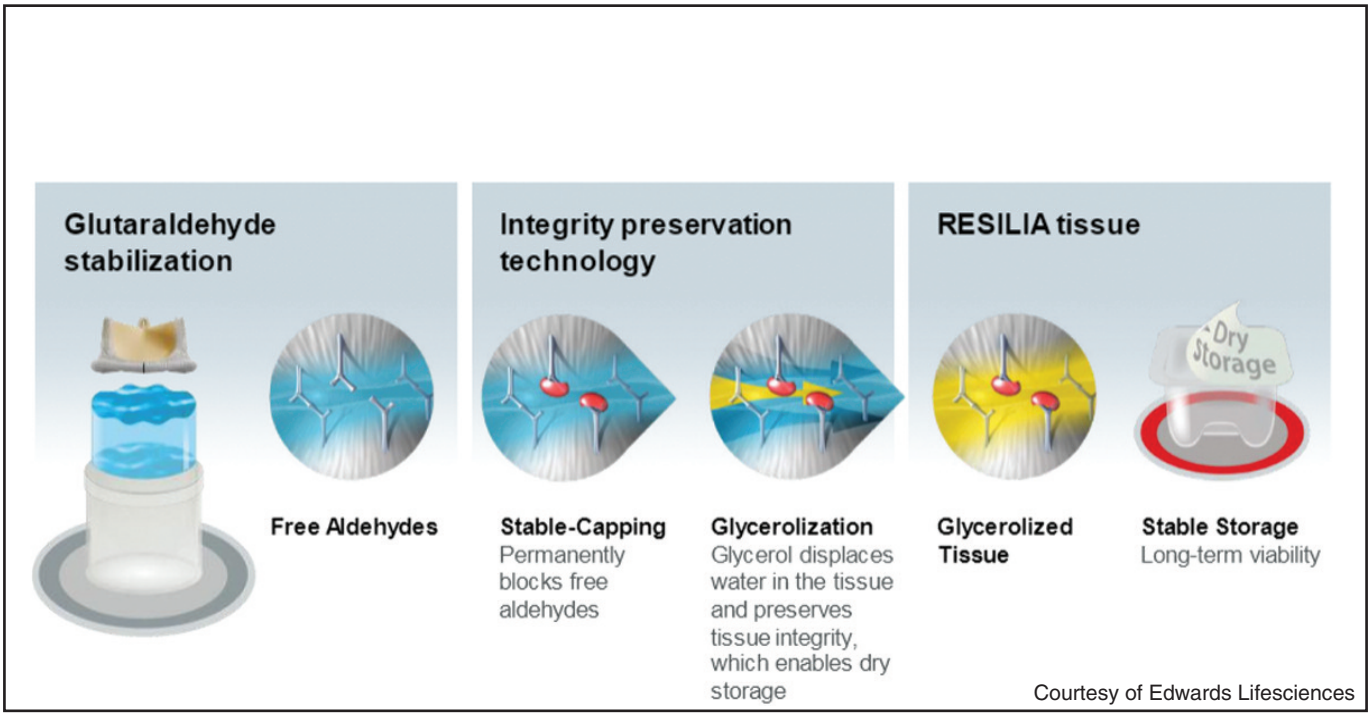

Figure 2. Resilia (Edwards) stabilization and production steps.

inspiring name "COMMENCE" (nearly 700 all-comer patients in 27 centers). These pivotal studies led to approval by regulatory agencies (CE in Europe and FDA in North America) in 2017, opening the door for "real world" studies.

Three major studies are currently underway (producing interim analysis data): the RESILIENCE study, started in 2018 with a plan to enroll 250 patients under the age of 65 at 15 centers, with planned interim analyses at 5, 7, 9 and 11 years; the INDURE trial, started in 2019 with a plan to enroll 400 patients under the age of 60 at 21 centers; and the IMPACT trial, started in 2020 with a plan to enroll 500 all-comer patients at 22 centers.

Conclusive pivotal trials reported the safety and effectiveness of RESILIA tissue, and provided consistent results compared to the early and intermediate findings.[1-4] The RESILIA European Study (133 patients, mean age 65.3 ± 13.5 y) and the COMMENCE aortic trial (689 patients, mean age 66.9 ± 11.6 y) reported 0% structural valve degeneration at 5 years of follow-up.[5,6]

To date, only 1 of the more than 800 patients enrolled in the above-mentioned clinical trials has been reported to show structural valve dysfunction (SVD) after 5 years.[6] The RESILIENCE study is currently enrolling patients who have reached a minimum of 5 years from surgery, and will continue up to 11 years of follow up.[7]

The preliminary results of the INDURE multicenter prospective registry were presented at the EACTS meeting in Barcelona in 2021. The protocol of the INDURE registry was published in 2020.[8] The registry enrolled 435 patients in 21 hospitals across Europe and Canada. The INDURE registry confirmed that the INSPIRIS RESILIA aortic valve provided satisfactory safety and effectiveness in a low-risk population under the age of 60 (mean age 53 y; EuroSCORE II 1.7 ± 1.7). Patient outcomes were reported according to VARC 2 criteria, and Echo Core Lab-adjudicated; 30-day all-cause mortality

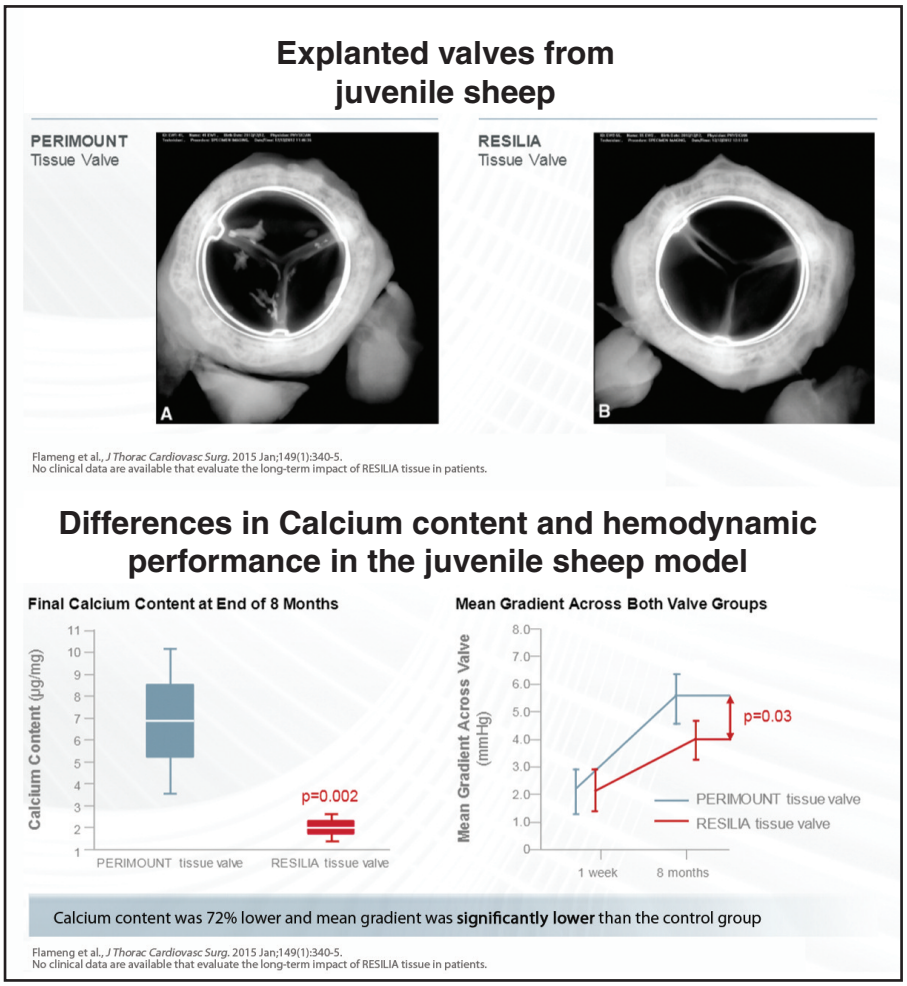

Figure 3. Explanted Resilia (Edwards) valves from sheep models.

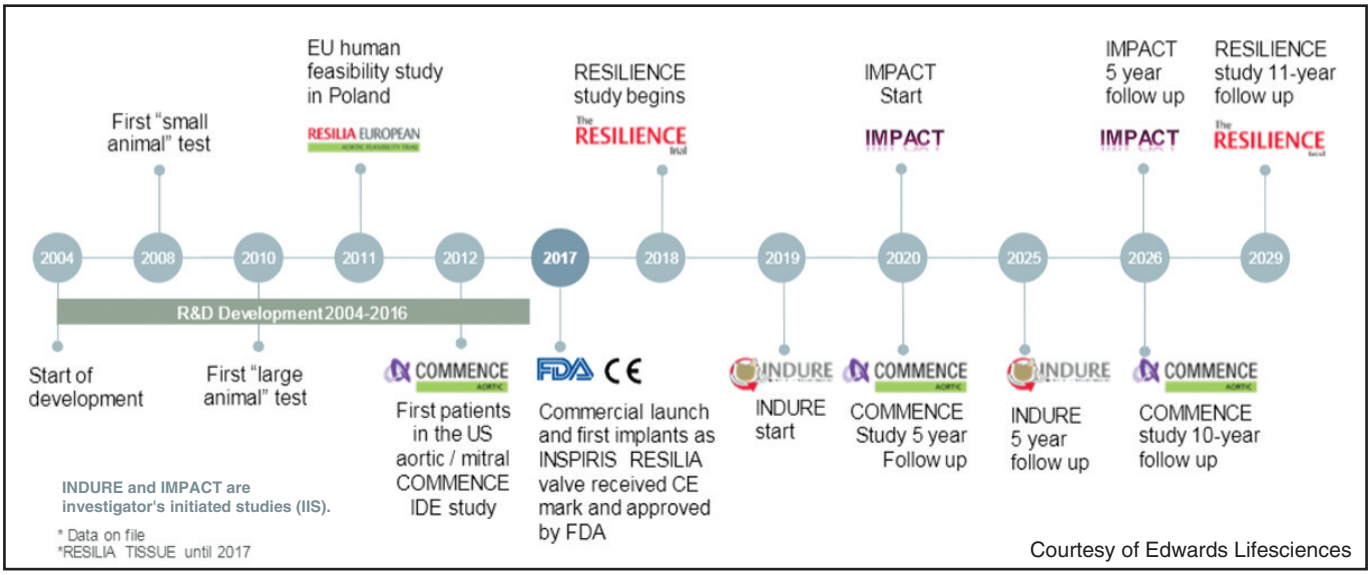

Figure 4. Timeline of animal and human studies.

was roughly 1%. Follow-up will continue up to 5 years.

One interesting dynamic is the increasing degree of confidence shown targeting progressively younger patients, in whom the challenge of calcification matters the most. However, all of these studies are still prospective observational trials, which will rely on historical data for comparison. Therefore, an internal comparison with the Perimount valve will be mandatory to better evaluate the real advantage of this new valve tissue in the real world.

Figure 4 shows a timeline of presently available and ongoing evidence.

In-hospital results – The European Hospital experience

The first implant of an Inspiris Resilia (Edwards) prosthesis was performed in our center in July 2017, in a male patient, with a 27 mm prosthesis. Many other implants have been performed before we became one of the main investigative centers for the INDURE study in Europe.

We enrolled the first patient for the INDURE trial in May 2019, and completed enrollment in December 2020, accounting for a total of 30 patients.

The total number of implants as of November 2021 was 248, with a trend for larger-volume implants over time (Fig. 5). The mean age of the patients was 59 ± 32 years; 79% (193 pts) were males, and the average size of the implanted prosthesis was 23 ± 2.23. The procedures were isolated in 43%, and combined in the remaining 57%. Early mortality was observed in 1.13% (3 pts). The pacemaker implantation rate was 2.26% (6 pts), and extracorporeal circulation (ECC) and crossclamp times were respectively 89 ± 32 min and 71 ±24 min, which are not significantly different from those in our standard procedure.

Four patients (1.69%) were operated on under emergency conditions, while six patients (2.26%) were reoperations. Replacement was carried out as an isolated procedure in 106 patients (42.94%).

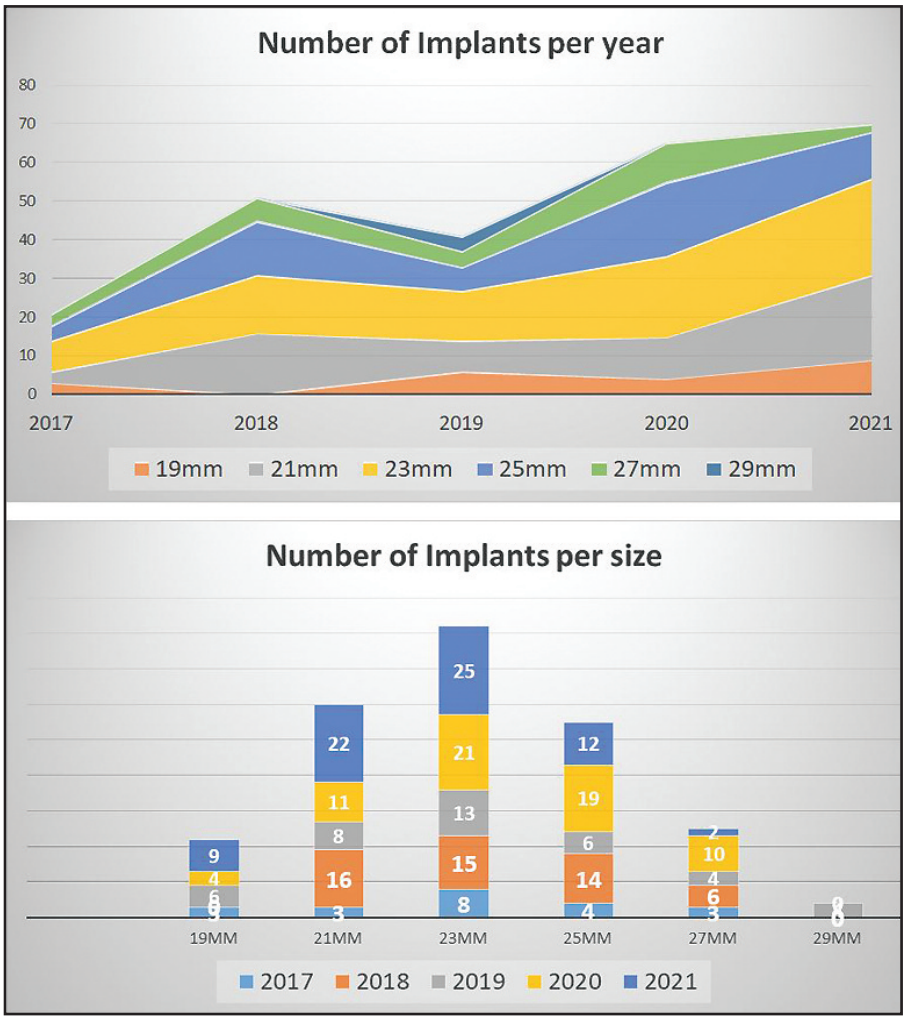

Figure 5. European Hospital experience with the Inspiris Resilia (Edwards) prosthesis. (a) implants according to year; (b) implants according to size.

CONCLUSION

A discussion of the impact of a new technology requires a broad view. It is not just a matter of raw results, but should also be considered as part of a bigger picture involving human expectations and perceptions regarding quality of life. At least three points should be considered:

1. Technical fact: Recent progress in anticalcification treatment has clearly led to an improvement in the prevention of structural valve dysfunction (SVD), with Resilia tissue (Edwards) showing the best results, in both lab testing and international studies of implants in humans. This means that even mitral prostheses should benefit from this "calcification slow down", allowing a longer durability and anticoagulation-related event-free life in a wider range of patients. Theoretically, no biological prosthesis will ever match a mechanical prosthesis in terms of longevity, but they can certainly reduce the long-term risk of anticoagulation therapy.
2. Cultural evidence: In the western world, we now accept the compromise of a longer life at the cost of surgical interventions, all risks inclusive. Thus, the acceptance of a temporary biological valve and a second lighter intervention is no longer a scary option. We have all seen how much our patients, especially younger patients, desire a good quality of life, and this has reduced the age limit for the implantation of biological prostheses.
3. Interventional skills: Advances in transfemoral prosthesis implantation for aortic valve disease (TAVR) have displaced surgery from a preeminent position in the treatment of valve pathology, and it is no longer mandatory for patients to undergo surgery. However, more interesting is the availability of Valve-in-Valve (ViV) implantation, which is a good alternative to the use of a mechanical prosthesis at the time of the first operation.

Over the past few years, the approach to patients with heart valve diseases has changed, and has certainly been enriched by a series of increasing opportunities. The need for a second surgical procedure is certainly decreased compared to only a few years ago.

In conclusion, the availability of biological valves with a potentially longer durability will progressively modify the choices of surgeons and patients, both always aiming to achieve a better quality of life free of medical therapy. Results with implants in younger patients are particularly important to ascertain if this expectation can be realized. In the meantime, we welcome another option for all patients suffering from heart valve diseases. STI

AUTHORS' DISCLOSURES

AR and RDP have received grant support from Edwards Lifesciences (Irvine, CA) as investigators in the INDURE trial. The other authors declare that there are no conflicts of interest.

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