Received: 11 January 2021 | Revised: 23 March 2021 | Accepted: 18 April 2021

DOI: 10.1111/jocs.15604

REVIEW ARTICLE

JOURNAL OF CARDIAC SURGERY WILEY

Fifty years of the pericardial valve: Long-term results in the aortic position

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Abstract

It is now 50 years since the development of the first pericardial valve in 1971. In this time significant progress has been made in refining valve design aimed at improving the longevity of the prostheses. This article reviews the current literature regarding the longevity of pericardial heart valves in the aortic position. Side by side comparisons of freedom from structural valve degeneration are made for the valves most commonly used in clinical practice today, including stented, stentless, and sutureless valves. Strategies to reduce structural valve degeneration are also discussed including methods of tissue fixation and anti-calcification, ways to minimise mechanical stress on the valve, and the role of patient prosthesis mismatch.

KEYWORDS
aortic valve, clinical review, pericardial heart valve

1 | INTRODUCTION

Since the development of the first pericardial heart valve by Marian Ionescu in 1971 the speciality has looked to develop a pericardial heart valve that will last the lifetime of the patient.[1] The Ionescu-Shiley Pericardial Xenograft valve consisted of three leaflets of bovine pericardium mounted on a titanium stent. In the later Ionescu-Shiley low-profile valve, Titanium was replaced by Delrin to increase the stents flexibility and optimise haemodynamics.[2] Early studies reported favourable rates of thromboembolism and improved haemodynamics when compared to existing porcine valves.[3] However, valve failure both in terms of regurgitation and calcification was seen to increase from the 6th year onwards.[4] Leaflet rupture occured at the point of the cusp commissural sutures that were used to align the leaflets in this particular valve design.[5] The second generation of pericardial valves sought to modify Ionescu's original concept to avoid structural valve degeneration (SVD) and increase valve longevity. In addition to the design of the valve, intraoperative and postoperative strategies of increasing valve longevity have been investigated.

2 | MINIMISING STRUCTURAL VALVE DEGENERATION IN THE AORTIC POSITION

SVD is the primary cause of failure in bioprosthetic valves and results mainly from cuspal degeneration; either due to leaflet calcification causing stenosis or leaflet tears resulting in regurgitation. As such, strategies to combat SVD in pericardial valves have focused on two main areas. Firstly, developing anti-calcification treatments to prevent or slow leaflet calcification and secondly, modifying the method of leaflet suspension to improve haemodynamics and minimise mechanical stress.

2.1 | Tissue fixation and anti-calcification treatments

Pericardial valves undergo two main processes to protect against SVD due to collagen deterioration and anti-calcification. Nearly all current commercially available bioprosthetic valves utilise glutaraldehyde (GA) fixation. In GA fixation, treatment with 0.625% glutaraldehyde results in collagen cross-linking, protecting the tissue from proteolytic degradation when implanted and lowering its antigenicity.[6,7] This method of tissue fixation has remained relatively unchanged from the first generation of tissue valves, although the fixation pressures have changed over time.

The first pericardial valves to be developed underwent GA fixation at high back pressures of approximately 80 mmHg. Subsequent bench testing of porcine valves fixed at high pressure showed that this results in stiff noncompliant leaflet material that has a tendency to kink.[8] These kinks caused sites of local strain that were thought to be the cause of early leaflet rupture in the first generation of pericardial valves.[9] In further bench testing, Broom et al. demonstrated that 'low-pressure fixation' at 4 mmHg was sufficient to cause coaptation of the valve leaflets whilst the reduced pressure resulted in improved compliance of the leaflets and lower internal stresses on the leaflets.[8] As such "High-pressure-fixation" was abandoned for the second generation of pericardial valves from the 1980s onwards. The majority of valves in use today employ low pressure GA fixation to preserve the pericardial leaflet tissue. Medtronic developed a system of zero-pressure fixation in their 'Intact' porcine valve in which the leaflets were fixed without coaptation in an unpressurised root.[10] However, there is no clinical evidence that this process improved either the haemodynamics of the valve or is longevity, with the valve being more prone to SVD than established pericardial valves in the market with a 10 year freedom from explantation of just 64%.[11]

Despite GA fixation there is evidence that implanted pericardial tissue continues to elicit an immune response in the recipient that might contribute to early calcification and failure.[12] The GA fixation process leaves residual free aldehyde components and phospholipids which can act as binding sites for calcium, leading to early, severe calcification if left untreated.[13] Different pericardial valve manufacturers have adopted different anti-calcification treatments to combat this issue. Edwards Lifesciences manufacture the well-established Perimount bovine pericardial valve. This valve originally employed the XenoLogiX tissue treatment which utilised a two-step process to remove phospholipids from the leaflets. Cunanan et al. demonstrated that this treatment removed more than 90% of the phospholipids from the leaflets which act as binding sites for calcification.[14] Over the last 30 years Edwards have evolved their anti-calcification processes. The Thermafix (TFX) method uses buffered glutaraldehyde and formaldehyde-Tween 80 solution (FET) to sterilise, fix, and reduce the antigenicity of the pericardial leaflets.[15] This process has been utilised in the Perimount Magna Ease tissue valve.

In a more recent advancement, Edwards have developed a new treatment based on capping the free-aldehydes to permanently block any interaction with calcium. The tissue then undergoes glycerolisation so that any residual water molecules are replaced with glycerol. Use of this tissue (termed Resilia tissue) in a Perimount valve resulted in a 72% reduction in calcium when compared to a TFX treated valve in a juvenile sheep model.[16] The COMMENCE trial implanted Perimount Magna Ease valves modified to encorporate Resilia tissue into 689 patients between 2013 and 2016.[17] Four year follow up data showed favourably safety and haemodynamic performance with effective orifice areas of 1.5 ± 0.5 cm^2, mean gradients of 11.0 ± 5.6 mmHg and no cases of SVD.[18]

St Jude medical manufacture the Trifecta bovine pericardial aortic valve. This valve uses Linx anti-calcification technology, an ethanol based process shown to reduce leaflet calcium by four mechanisms; the extraction of lipids, reduction of free aldehydes, minimisation of cholesterol uptake, and stabilisation of leaflet collagen.[19,20] The removal of lipids, free-aldehydes and cholesterol reduces the number of potential calcium binding sites.

LivaNova (formally Sorin) manufacture the latest fourth generation model of the Mitroflow pericardial aortic valve, termed the CROWN-PRT (Phospholipid reducing technology). This treatment uses Octanediol to interact with phospholipids within the leaflets making them water soluble an thus able to be rinsed off on washing. This process was seen to reduce the calcification of bovine pericardium by 97% at 60 days in an in vivo rat model.[13]

2.2 | Mechanical stress

It was initially thought that mechanical cusp failure and leaflet tearing were a result of the calcification process. However, non-calcific degeneration is now also thought to occur as a result of mechanical stresses due to the absence of physiological repair mechanisms in the implanted tissue.[21] Histological examination of explanted porcine bioprosthetic valves have shown free-edge tears in the absence of calcification at points that experience the highest localised mechanical forces.[22,23] Tears are associated with collagen fibre degradation. As such successive iterations of the pericardial valve have attempted to minimise mechanical sheer stress on the valve leaflets whilst simultaneously ensuring optimal haemodynamic performance. In stented valves, the primary site of leaflet tears occurs at their commissural attachment to the stent. In modern pericardial valves, three near cylindrical sheet leaflet designs produces a near straight free edge during coaptation. This configuration generates maximal sheer stress at the leaflet free edge at the commissural attachment to the stent. Reducing the angle of the free edge away from the horizontal is not practical as, although this reduces the mechanical stress on the leaflet, it also reduces the coaptation zone of the relatively stiff glyceraldehyde fixed leaflets resulting in leakage. It is possible to reduce the mechanical stress on pericardial valves by designing the leaflets so that they lean against each other during closure. The disadvantage of this design is that if one leaflet degenerates and starts to prolapse then it ceases to provide the opposing force on the other two leaflets. This in turn raises the peak

tensile loads on the other leaflets and accelerates degeneration of the valve. With the above in mind several designs have been developed to minimise mechanical stress on the valve leaflets including; mounting the leaflets external to the stent to minimise impingement on valve opening, single pericardial sheet valves (to reduce the number of sutured attachments), and cross-stitched commissural attachments to distribute stress evenly.

A further modification in pericardial valves from the Ionescu-Shiley valve is the development of flexible stents. Early designs of bovine pericardial valves used rigid stents posts. After early reports of leaflet tearing of the commissural attachments to the posts it was thought that the rigidity of the posts was to blame. Computational modelling was used to demonstrate a theoretical advantage of flexible stents,[24] resulting in a shift in valve design. Such stents proved a challenge for valve design as leaflet sizing and positioning must take into account the variable positions of the stent to ensure sufficient coaptation of the leaflets in diastole whilst avoiding redundancy in systole. Due to the absence of control data the benefit of flexible stents has not been proven in terms of real-world improved valve longevity.

2.3 | Patient-prosthesis mismatch

Since Rahimtoola first introduced the concept of patient prosthesis mismatch (PPM) in 1978 opinion has been split regarding its prognostic significance. PPM occurs when a valve's effective orifice area (EOA) indexed for body surface area (BSA) is less than that of a native valve. The threshold for PPM is defined as an indexed EOA < 0.85cm^2/m^2. Whilst some reports describe an association with reduced short and long term mortality this has not been consistently demonstrated. However, several studies have described the presence of PPM as an independent risk factor for the subsequent development of early structural valve degeneration. Flameng et al. showed that moderate or severe PPM was associated with a significant increase in the rate of SVD over a median follow up period of 6 years.[16] Furthermore they were able to demonstrate that SVD was more often due to stenosis in the presence of PPM whereas with no PPM it was more likely due to regurgitation. In a later report, the authors performed a multivariate analysis for valve related predictors of SVD and demonstrated that anti-calcification techniques, and the presence of PPM were independent predictors of subsequent SVD.[25] In a sub-group analysis PPM was only found to be a predictor of stenotic-SVD and not regurgitant-SVD. More recently, Urso et al. confirmed these findings showing that patients with PPM were twice as likely to undergo reoperation for aortic valve replacement for SVD than those without.[26]

2.4 | Antithrombotic therapy postimplantation

Antithrombotic therapy following pericardial aortic valve implantation is aimed at preventing valve thrombosis and reducing the incidence of thromboembolic complications. The current American Heart Association (AHA) guidelines on the management of valvular heart disease give a class 2a recommendation for the use of low dose antiplatelet agents following bioprosthetic AVR.[27] Randomised controlled trials have failed to demonstrate any benefit of anticoagulation over low dose antiplatelet therapy in the first 3 months following surgery in terms of mortality, thromboembolic complications or bleeding events.[28] This is perhaps not surprising given the relative rarity of such complications and the number of patients required to sufficiently power such a comparison. However, a large observational trial of 25 656 from the Society of Thoracic Surgeons national database showed similar findings.[29] A registry study of 4075 patients found that treatment with warfarin up to 6 months post-bioprosthetic AVR was associated with reduced cardiovascular death, although the groups were compared only on the basis of warfarin or no warfarin therapy without consideration of any antiplatelet use.[30] As such, the use of warfarin up to 6 months following bioprosthetic AVR is also given a class 2a recommendation in the recent AHA guidelines.[27]

3 | EVIDENCE FOR LONGEVITY OF PERICARDIAL HEART VALVES

Of the many pericardial valves that have been developed since Ionescu's first bovine pericardial valve, only a handful have stood the test of time. In this chapter, we will focus on the long-term results of pericardial valves in common use today including stented, stentless, and sutureless models. It is hard to make direct comparisons between different pericardial heart valves in terms of their freedom from SVD. Dvir et al. attempted to standardise the reporting of SVD but definitions remain heterogenous in the literature with the need for repeat valve replacement, echocardiographic findings, increase in valve gradients, or findings at autopsy all being reported.[31,32] The methods of reporting SVD also differ with the majority of studies reporting actuarial rates of SVD whilst others report actual rates. The actuarial rate of SVD is the rate assuming that all patients survived to be able to experience valve degeneration whilst the actual rate is the percentage of patients whose valve will actually fail before they die.[33]

4 | STENTED VALVES

Of the stented aortic valves in place today the most commonly used are the LivaNova (formerly Sorin) Mitroflow aortic valve, the Edwards Perimount valve, and the St Jude Trifecta valve (Figure 1). Table 1 shows the rates of SVD in the larger studies reporting on longevity of each of these stented pericardial valves. Given the abundance of studies into the longevity of stented pericardial valves, we have included studies of >500 participants and with follow up periods of >2 years.

The Mitroflow aortic valve consist of a single sheet of bovine pericardium externally mounted to the outside of an acetyl

TABLE 1 Studies into the longevity of stented pericardial valves in the aortic position

Valve type	Authors	Year	Number of patients	Date range	Mean age	Actuarial freedom from SVD	Additional results
Mitroflow	USA FDA	2007	699	Na	74.3	2 years: 99.4%	
	Mosquera et al.[29]	2016	1023	2001–2014	75.6	1 year: 99.5%	
						5 years: 97.4%	
						10 years: 88.2%	
	Conte et al.[28]	2010	689	2003–2007	74.3	3 years: 99.2%	
	Senage et al.[32]	2014	617	2002–2007	76.1	5 years: 91.6%[a]	39 cases of SVD.
							4 reoperated
	Piccardo et al.[31]	2016	728	1994–2011	76	10 years: 77%[a]	30 patients had SVD on TTE.
						15 years: 56%[a]	8 reoperated
	Minami et al.[30]	2005	1516	1985–2004	Not reported	5 years: 99%	84 patients with SVD.
						10 years: 82.8%	51 reoperated
						15 years: 62.8%	
	Narayanan et al.[34]	2015	1003	2004–2011	74.8	5 years: 93.8%	12 reoperated
	Yankah et al.[35]	2008	1513	1986–2007	73.2	20 years: 62.3%	64 reoperated
Perimount	Johnston et al.[33]	2015	12569	1982–2011	71	10 year: 98.1%	156 reoperated for SVD
						20 years: 85%	
	Bourguignon et al.[36]	2015	2659	1984–2008	70.7	20 years: 54.3	
	Chan et al.[37]	2010	638	1990–2007	73.2	10 years: 97.2%	
	Forcillo et al.[38]	2013	2405	1981–2011	71	5 years: 98%	
						10 years: 96%	
						20 years: 67%	
	Jamieson et al.[39]	2006	1430	1981–1999	68.9	15 years: 87.7%	
Perimount MagnaEase	Anselmi et al.[40]	2019	849	2008–2015	75.4	5 years: 98%	No early SVD
							6 SVD at mean 3.4 yrs (5 reoperated).
Trifecta	Anselmi et al.[41]	2017	824	2008–2014	75	5 years: 98%	5 reoperated
	Bavaria et al.[42]	2014	1014	2007–2009	73	2 years: 99.4%	1 reoperated
	Fukuhara et al.[43]	2020	508	2011–2015	70	3 years: 98.8%	
						5 years: 97.9%	
						7 Years: 86.7%	
	Goldman et al.[44]	2017	710	2007–2009	72	6 years: 95.7%`	11 reoperated
	Kilic et al.[45]	2019	1953	2011–2017	72	5 years: 98.7%	12 patient reoperated
	Lehman et al.[46]	2020	1241	2007–2018	72	5 years: 98.7%	30 patients with SVD
						8 years: 93.3%	All reoperated.
	Raimundo et al.[47]	2018	556	2011–2016	73	-	2 SVD at mean follow up of 27 months

Abbreviation: SVD, structural valve degeneration.

[a]Based on echocardiographic data rather than reoperation.

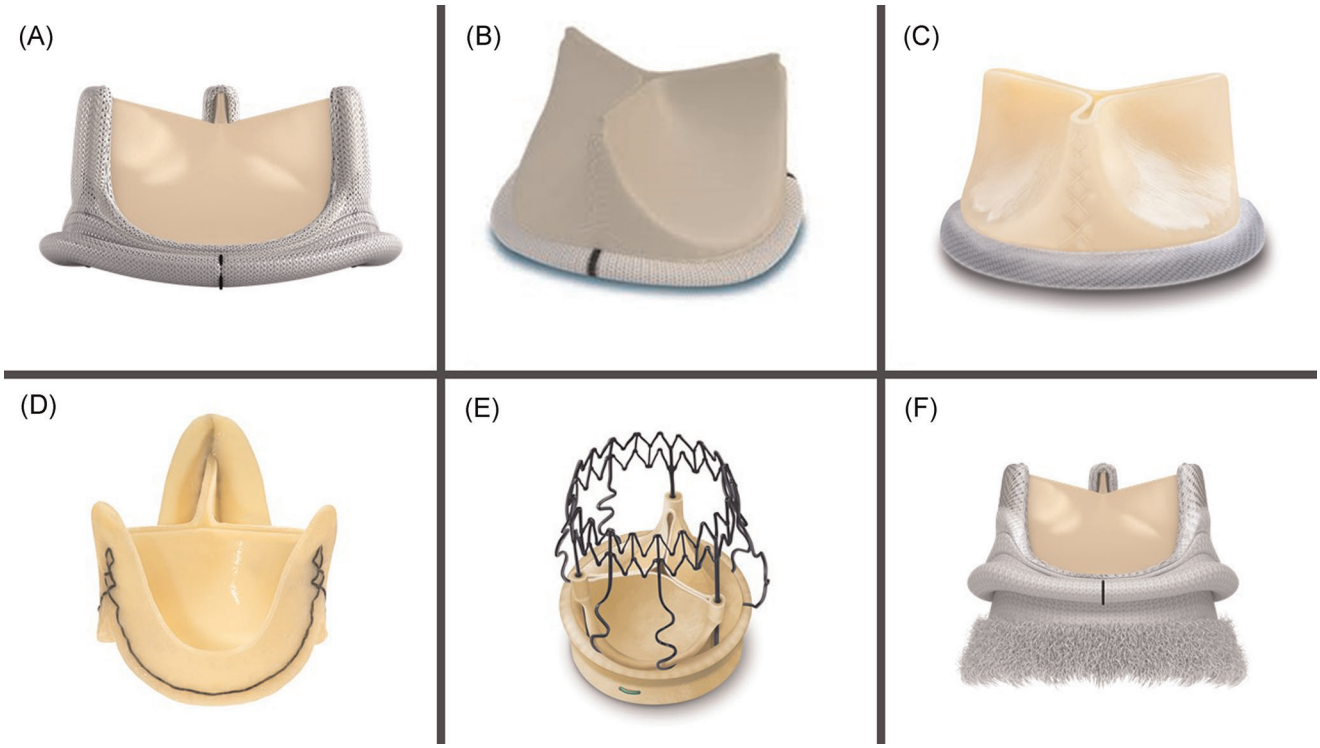

FIGURE 1 Pictures of the various pericardial aortic valves commonly in use. A = Perimount Magna Ease; B = Trifecta; C = Mitroflow; D = Freedom SOLO valve; E = Perceval Sutureless Valve; F = Intuity Sutureless Valve. Trifecta and Glide are trademarks of Abbott or its related companies. Reproduced with permission of Abbott, © 2021. All rights reserved. Edwards, Edwards Lifesciences, Carpentier-Edwards, Magna, Magna Ease, PERIMOUNT Magna, and EDWARDS INTUITY Elite are trademarks of Edwards Lifesciences Corporation. Reproduced with permission of Edwards. Mitroflow, Perceval and Freedom SOLO images reproduced with permission of LIvaNova

homopolymer stent. It was first introduced in Europe in 1982 but only approved for the US market in 2007. In the years since its initial development it has undergone several iterations with modifications aimed at improving its longevity. The latest of these added the PRT anti-calcification treatment previously discussed. Initial reports of longevity with the Mitroflow aortic valve were promising with several studies showing excellent freedom from SVD ranging from 99.5% at 1 year to 99% at 5 years.[36,48,49] However, later studies show that after 5 years the rate of SVD increases significantly. Three studies report 10 year actuarial freedom from SVD as ranging from 88% down to 77% with two of these reporting 15 year figures of 56% and 62.8%.[48–50] Yankah et al. report on a single centre cohort of 1513 patients with a 20 year freedom from SVD of 62.3%. One further study, by Senage et al.[41] reports a concerning trend in early valve failure from SVD with a 5 year freedom from SVD of only 91.6%. A potential cause of this finding is that this study defines SVD by echocardiographic criteria rather than at time of reoperation. However, due to the consistent findings of increased rates of SVD between 5 and 10 years from operation, the Mitroflow valve has become less prevalent in current clinical practice.

Shortly after the introduction of the Mitroflow, the Edwards Perimount valve was first introduced in 1984. The first generation Perimount was a bovine pericardial valve supported by a flexible stent of cobalt-chromium alloy. Long term data is available for valve function over >20 years of follow up. Johnstone et al. report on 12,569 between 1982 and 2011 and report an actuarial freedom from reoperation for SVD of 98.1% at 10 years and 85% at 20 years overall. In patients less than 60 years actuarial freedom from re-operation for SVD was 94.4% at 5 years, 80% at 10 years, and 55% at 20 years.[46] Similar results are reported in 2659 patients with a 54.3% actuarial freedom of explant for SVD at 20 years.[42] In the longest follow up reported to date, Forcillo et al. report on 25 year experience of the Permount valve. Age at implantation was the strongest predictor of SVD. Actuarial rates for freedom from re-operation for SVD at 20 years were 67% overall dropping to 30% patients <60 at operation. In patients aged 60–70, 15 year freedom from reoperation was an impressive 90%. In patients >60 years of age, there is consistent evidence of excellent freedom from SVD for the first generation Perimount valve.

Edwards have made progressive evolutions to the base Perimount pericardial valve whilst keeping the basic principles the same. In 2003, the US FDA approved the CE Perimount Magna aortic valve. The Magna valve differs from the standard Perimount in that it is designed to be placed in a supra-annular position To maximise its haemodynamic properties and increase the EOA of the valve. Both of these valves are treated with Edwards' XenoLogiX tissue treatment. A further iteration termed the Perimount Magna Ease received FDA approval in 2009. The Magna Ease is a lower profile version of the

supra-annular Magna valve with the addition of Thermafix anti-calcification treatment to the leaflets.

The St Jude Trifecta valve is a trileaflet stented valve designed for supra-annular placement in the aortic position. It is comprised of a polyester covered titanium stent which is then covered in porcine pericardium (excluding the sewing ring). Bovine pericardial leaflets are attached to the exterior portion of the stented valve allowing fuller opening of the valve in systole. The Trifecta valve was introduced into clinical practice in 2010 and as such there is a lack of data on its long-term durability. Early studies into its haemodynamic performance showed favourable transvalvular gradients and indexed EOA's to both the Mitroflow and the Perimount valves.[43,44] However, Wendt et al. showed no significant difference in mean gradient or valve area between the Trifecta and Perimount valves after multivariate modelling.[39] It was hoped that improved early haemodynamics would translate into improved long-term durability as studies have found that postoperative transvalvular gradient and degree of patient-prosthesis mismatch are predictors of early structural valve degeneration.[51] Early reports of the durability of the Trifecta valve were encouraging. Anselmi et al. report a 98% freedom from structural valve degeneration at 5 years with similar results reported by Lehman et al. (98.7% freedom from SVD at 5 years) and Bavaria et al. (99.4% freedom form SVD at 2 years).[52–54] However, Goldman et al. report a 6 year freedom from SVD of just 95.7% whilst Fukuhara et al. report a cumulative incidence of SVD at 7 years of 13.3% with the Trifecta valve.[55,56] Reports such as these have led the cardiac surgical community to look harder at the durability of the Trifecta valve resulting in several recently published comparative studies of its longevity versus that of the Perimount valve.

4.1 | Comparative studies of the durability of pericardial valves in the aortic position

Studies into the longevity of the more recent pericardial valves, such as the Magna Ease and the Trifecta, have tended to be performed as comparative studies. It should be noted that none of these comparative studies are randomised controlled trials. Rather, the majority are retrospective analyses of prospectively collated databases and as such are subject to the usual biases of non-randomised studies. Whilst attempts have been made to control for confounders by propensity matching or multivariate analyses it may be that inherent differences persist between the valve cohorts.

Whilst early studies showed improved haemodynamics of the Trifecta over the Perimount aortic valve, these initial benefits did not translate into long-term improved function. Yongue et al. demonstrated in >2000 Trifecta patients that mean gradients increased quicker over time than with the Edwards Perimount valve with the initial advantage of the Trifecta being lost before 5 years of follow up. Furthermore the majority of cases of SVD requiring reoperation were caused by restenosis and pannus formation rather than regurgitation from leaflet disruption. This higher rate of restenosis with the Trifecta valve is thought to underlie the higher rates of reintervention for SVD in patients treated with a Trifecta valve in comparative studies with the Perimount valve (Table 2). The same study reports a freedom from reoperation for SVD of 95.9% with the Trifecta valve compared to just 98.7% with the Perimount valve. In addition, the Perimount valve has been shown to have superior longevity in comparison to both the earlier Carpentier Edwards Porcine Supra-annular valve (15 year freedom from SVD or 87.7% vs. 75.1%),[58] and the Mitroflow pericardial valve (5 year freedom for SVD of 100% vs 96%).[59]

TABLE 2 Comparative studies into the longevity of stented pericardial valves in the aortic position

Authors	Year	Date range	Valve type	Number of patients	Mean age	Reported rates of structural valve degeneration
Lam et al.[52]	2020	2009–2018	Trifecta	719	71.6	Fourteen (1.9%) reintervention rate for SVD at mean 4.1 years.
			Mitroflow	362	72.0	Fourteen (3.9%) reintervention rate for SVD at 4.1 years
			Perimount Magna Ease	923	71.2	Zero re-intervention for SVD at 4.1 years
Biancari et al.[53]	2020	2008–2017	Trifecta	851	74	7 years: 3.3% reoperated for SVD
			Perimount Magna Ease	1365	73.9	7 years: 0% reoperated for SVD
Yongue et al.[57]	2020	2007–2017	Trifecta	2298	69	5 years: 95.9% freedom from SVD
			Perimount	2298	70	5 years: 98.7% freedom from SVD
Neilsen et al.[51]	2016	1999–2014	Mitroflow	440	76.2	10 years: 95.6% freedom form SVD
			Perimount	1953	74.4	10 years: 99.5% freedom form SVD

Abbreviation: SVD, structural valve degeneration.

The same trend is seen with the later iterations of the Perimount valve. In a comparative study of 923 Perimount Magna Ease aortic valves, 719 Trifecta valves and 362 Mitroflow prostheses, the Magna Ease was found to be significantly associated with improved freedom from SVD.[60] The only cause of reintervention in the Perimount group was for endocarditis with no cases of SVD over a mean follow up of 49.2 months. This compared to 14 cases of SVD (1.9%) in the Trifecta group and 14 cases (3.9%) in the Mitroflow group over the same time period. On multivariate analysis, type of prosthesis was an independent predictor of lower event free survival (Trifecta: HR, 6.3; 95% CI, 2.6–15.2; $p < .0001$; Mitroflow: HR, 6.0, 95% CI, 2.415.1; $p < .0001$. Similar findings were reported by Biancari et al. in a propensity matched analysis of 772 paired Magna Ease and Trifecta valves. The risk of reintervention for SVD was significantly higher in the Trifecta cohort (5.7% vs. 0%; $p = .009$) despite lower postoperative mean gradients and lower incidence of patient-prosthesis mismatch.[61]

5 | STENTLESS VALVES

The first pericardial stentless valve, the Pericarbon Freedom (PF) was introduced in 1991. It was hoped that stentless valves would better mimic the native aortic valve and provide better haemodynamics by removing the resistance to flow conferred by a fixed stent. Furthermore a flexible, dynamic aortic root was thought to be essential for equal distribute and reduce stress across the three leaflets. In 2004, the PF valve was updated to sit in a supra-annular position as well as receiving anti-calcification treatment. This new valve, termed the SORIN freedom SOLO (FS), showed excellent haemodynamic profiles postimplantation that were favourable to many of the more established stented valves. Repossini et al. report Echocardiographic data over 10 years of follow up showing mean gradients of 9.9 mmHg (±5.4) postoperatively and 9.6 mmHg (±3.7) at 10 year follow up.[62] However in a propensity matched comparison with the Trifecta Valve the FS actually demonstrated slightly worse haemodynamics with marginally greater mean transvalvular gradient and lower iEOA.[63]

To achieve widespread uptake, stentless valves must demonstrate at least non-inferiority to currently available stented valves in terms of long-term clinical outcomes. The FS valve only achieved FDA approval in 2014 and the number of studies reporting long-term outcome data are limited. Data on freedom from SVD for the FS valve is shown in Table 3. Evidence for the longevity of the Freedom SOLO valve is mixed with reported 10 year freedom of SVD ranging from 92% to as low as 70%.[62,66,67] As such, the current evidence suggests that the longevity of the FS salve is inferior to that of commonly used stented valves, particularly that of the Edwards Perimount.

Stentless valves are more technically challenging to implant due to the fact that their optimal function and long-term durability is closely related to achieving a perfectly symmetrical valve within the aortic root. They are also not universally suitable for all cases and it has been suggested that they be avoided in patients with moderate aortic root dilatation and in bicuspid aortic valve (BAV) due to altered geometery of the aortic root. Furthermore, there are reports that redo-surgery in the presence of stentless valves is a more challenging and high risk procedure than for other biological valve prostheses due to dense adhesions and calcification between the stentless valve and native aortic root.[68]

When the above is considered in the context that new generation stented valves have similar haemodynamic profiles and equal or superior longevity, it is easy to see why such valves have not been widely accepted and utilised by the surgical community.

6 | SUTURELESS VALVES

Following the success of transcatheter aortic valve implantation (TAVI) it became apparent that it is possible to deploy aortic valves without the need to suture them in position. Sutureless or rapid deployment aortic valves were developed to bridge the gap between TAVI and conventional SAVR. Sutureless AVR provides a rapid method of inserting a surgical aortic valve that can minimise cross-clamp and bypass times whilst still providing the benefits of a surgical procedure in terms of excision of the existing valve with

TABLE 3 Studies into the longevity of the freedom SOLO stentless pericardial valve in the aortic position

Authors	Year	Number of patients	Date range	Mean age	Actuarial freedom from SVD	Additional results
Cerqueira et al.[55]	2018	329	2009–2016	74	Not reported	3 reoperated
Fleerakkers et al.[64]	2018	625	2009–2017	76	7 years: 98%	2 reoperated
Repossini et al.[54]	2016	565	2004–2009	75	10 years: 91.9%	18 reoperated
Wollersheim et al.[65]	2016	350	2005–2014	76	6 years: 98%	
Stanger et al.[56]	2015	149	2005–2009	74.2	10 years: 70%	
Sponga et al.[58]	2017	109	2004–2009	76	1 year: 99% 5 years: 93% 10 years: 76%	

Abbreviation: SVD, structural valve degeneration.

TABLE 4 Studies into the longevity of Sutureless pericardial valves in the aortic position

Valve type	Authors	Year	Number of patients	Date range	Mean age	Actuarial freedom from SVD	Additional results
LivaNova Perceval	Shrestha et al.[63]	2016	731	2007–2012	78.5	5 years: 100%	Nine early re-operations for mal-sizing (3), malpositioning (5) and bleeding (RCA ostial tear)
	Szecel et al.[66]	2020	468	2007–2009	79	10 years: 97%[a]	Nil reintervention for SVD
	Glauber et al.[67]	2020	480	2011–2018	76.1	2 years: 100%	Three late reinterventions for SVD
						6 years 99.5%	Seven early reinterventions for NSVD
Edwards Intuity	Laufer et al.[70]	2017	287	Not reported	75.3	Not reported	Four late cases of SVD – no reintervention required.
							Two early and three late reinterventions for NSVD
	Coti et al.[71]	2020	700	2010–2019	73.6	Not reported	Four late cases of SVD (2 reoperated)
							Eight early and 5 late reinterventions for NSVD
Medtronic Enable	Englberger et al.[62]	2014	141	2007–2009	76.1	100% at mean follow up of 2.7 years	Four late reoperations for NSVD

Abbreviations: SVD, structural valve degeneration; NSVD, nonstructural vale dysfunction.
[a]Based on echocardiographic data rather than reoperation.

reduced rates of paravalvular leak.[69] A primary reason for their development was the facilitation of minimal access aortic valve replacement.[70] Data on the longevity of the three sutureless valves currently in the market are discussed below (Table 4). These results should be viewed in the context that sutureless AVR is often performed in different clinical settings to that of SAVR with patients often being older, with greater co-morbidity and with a greater proportion of combined and minimally invasive procedures. In contrast to studies into stented valves, reports of long-term results of sutureless valves often comment on 'nonstructural valve deterioration'. As with SVD, the definition of NSVD varies across studies. It has been used variously to describe valve dysfunction arising from mal-sizing or malposition at the index operation or the presence of significant paravalvular leak.

The first sutureless valve to come to market was the Medtronic 3F Enable valve which received the CE mark in 2009. The Enable consists of equine pericardial leaflets mounted on a Nitinol stent and requires 1 guiding suture to be placed to aid deployment. The Nitinol stent is able to be recaptured to aid repositioning. Results up to 5 years have been reported[71] with a 5 year freedom from reoperation of 95.4 ± 6.1% and no cases of SVD reported. However, there were 4 cases of reoperation for NSVD. It's design requires a high aortotomy and there are anecdotal reports of difficulty with valve positioning. This is thought to have contributed to poor uptake of the valve in the surgical community resulting in Medtronic discontinuing production in 2015. A recent report on the outcomes of 432 implanted Enable valves confirmed low levels of morbidity and mortality at 30 days postimplantation but found a high pacemaker rate of 6.5%.[34]

The LivaNova Perceval sutureless valve received its CE mark in 2011 and was FDA approved in 2016. It is comprised of a bovine pericardial valve suspended within a stent made from a superelastic alloy (nickel and titanium construction). This stent is able to be compressed and return to its original shape. As such it can be crimped down on the holder before deployment. The stent consists of a proximal and distal anchoring ring together with connecting elements scalloped to mimic the sinuses of Valsalva. Three temporary guiding sutures are placed through three loops on the inflow ring to help guide the correct positioning of the valve. Once deployed the guiding sutures are removed and the valve is ballooned to secure it in place.

Early data for the first implanted Perceval valves date from 2007 and there are few studies detailing long-term outcomes after implantation. Shrestha et al. report on 731 patients with 0% SVD up to a maximum of 5 years follow up. However, it should be noted that 8 patients required early reoperations for nonstructural valve dysfunction including mal-sizing[3] and mal-positioning.[5,35] Scezel et al. describe their results in 468 patients at a single institution and report just 1 case of severe SVD at 7 years follow up resulting in a 97% freedom from SVD at 10 years.[37] A further 10 patients were found to have met the Dvir-criteria for moderate SVD with a mix of stenosis and regurgitation. However, none of the patients in the cohort underwent reoperation for SVD. Finally, Glauber et al. report the outcomes of 480 patients who underwent sutureless AVR with a

Perceval valve via a minimally invasive approach.[38] At 5 years follow up they report three cases of SVD (0.3%), 1 due to a cusp tear and one due to a calcified immobile cuff, both of which were treated by TAVI. The third resulted from a medically treated episode of infective endocarditis that progressed to a calcified valve requiring surgical replacement. There were also two cases of late NSVD, one due to rupture of the aortic annulus with pseudoaneurysm and the other due to worsening intra-prosthetic leak. As with the earlier report several patients were reoperated on with 30 days due the NSVD. Seven patients (1.3%) underwent re-intervention due to an early finding of severe regurgitation; six by reoperation (three valves repositioned, three explanted) and 1 by TAVI. An interesting finding from the early experience of implanting the Perceval sutureless valve is the need to accurately size the implant. Whilst under-sizing can result in paravalvular leak, over-sizing can prevent the valve from deploying fully. This can cause the stent to recoil and lose contact with the aortic wall, also resulting in paravalvular leak.[40] Furthermore, a partially deployed valve can lead to incomplete leaflet expansion and is associated with higher transvalvular gradients.[45]

Edward Lifesciences manufacture the Intuity valve; a rapidly deployable sutureless valve based on the well-established Perimount series of stented valves. As with the Perimount valves, the Intuity is made of bovine pericardial leaflets supported on a cobalt-chromium stent. The intuity valve is anchored with the aid of a balloon expandable stainless steel frame covered in a textured sealing cloth. Like the Perceval valve it requires loading onto a delivery system for deployment and balloon catheterisation to fix it in position. Three guiding sutures are placed to aid valve positioning which are tied after valve deployment. Unlike the Perceval, the delivery system does not result in folding of the valve leaflets themselves.

Laufer et al. report the 5-year outcomes of initial prospective trial designed to test the safety and efficacy of the Edwards Intuity valve.[47] Four cases of SVD are reported over the study period (0.4% per patient year (ppy)), none of which required reintervention. Three valves were explanted after 30 days and two before 30 days for NSVD (severe paravalvular leak). Coti et al. describe their single centre experience of implanting 700 Intuity valves with a median follow up period of 19 months (maximum 9 years).[57] There were four late cases of SVD (0.4% ppy); two of which required re-intervention with valve in valve (ViV) TAVI, one who died of heart failure, and one who did not require reintervention. In addition, there were five valve explantations for NSVD due to progressive paravalvular leak. These cases were in addition to 8 early valve explantations that were performed for malpositioning of the Intuity valve within 30 days of the index operation.

7 | A LOOK TO THE FUTURE

Stented pericardial valves remain the mainstay of bioprosthetic aortic valve replacement given their ease of implantation and proven durability out to 20 years of follow up. This durability is particular strong in patients over 70 years of age although more and more younger patients are opting for bioprosthetic valves. This is driven by their proven longevity together with the possibility of undergoing future valve-in-valve transcatheter procedures and avoiding the need for long-term anticoagulation. Aortic pericardial valves differ in their suitablility for valve-in-valve TAVI (ViV-TAVI) based on their effective orifice areas relative to their external diameter. Table 5 shows the differences in the effective orifice areas (EOA's) of the three main stented pericardial valve discussed in this review. The data shown is based on predischarge transthoracic echocardiography measurement.[43] Whilst the Trifecta valve has significantly larger EOA's relative to its external diameter, this has not yet translated into improved clinical outcomes. However, these differences may have implications for the feasibility of future ViV-TAVI procedures. In such instances the operator must consider the size and type of the in-situ pericardial valve as well as the size and type of the TAVI to be used. Apps have now been developed to help clinicians ensure that their chosen TAVI system will deploy inside the existing surgical valve.[64]

TABLE 5 Real world effective orifice area (cm^2) by valve type and size

Valve Size (mm)	Perimount Magna	Trifecta	Mitroflow
19	1.26	1.53	1.23
21	1.73	1.84	1.52
23	2.01	2.23	1.83
25	2.47	2.73	2.28
27	2.8	3.2	2.48

Note: Data taken from Ugur et al. JTCVS, 2014, Table 4. EOA was measured on predischarge transthoracic echocardiography.

The latest bioprosthetic valve from Edwards, the Inspiris resilia, is built specifically with future ViV-TAVI in mind, as it has a cobalt-chromium alloy stent designed to expand under ballooning to aid future valve in valve implantation. This valve also incorporates Edward's Resilia anticalcification treatment previously described. Currently no studies are available for the longevity of this valve but it is expected to perform at least as well as the Magna Ease valve on which it is based. The INSPIRIS RESILIA Durability Registry (INDURE) is currently collecting five year durability data on the use of the Inspiris Resilia valve in patients under the age of 60.[65]

Whilst stentless valves have not proved to be the panacea that they were originally thought to be, the use of sutureless valves is expected to increase if their longevity proves non-inferior to the current stented valves. At present, the literature available suggests that rates of SVD in sutureless valves is similar to that of stented valves, however there are higher rates of nonstructural valve dysfunction in the form of malpositioning and paravalvular leaks. It is thought that the frequency of nonstructural valve dysfunction will reduce with increased experience of sizing and positioning the valve correctly at time of implantation. If such predications are proved correct then sutureless valves provide attractive advantages of minimising ischaemic time and facilitating a move to more minimal access aortic valve surgery.

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How to cite this article: Balmforth D, Dimagli A, Benedetto U, Uppal R. Fifty years of the pericardial valve: Long-term results in the aortic position. *J Card Surg*. 2021;1-11.
https://doi.org/10.1111/jocs.15604