



Society for Cardiothoracic Surgery in Great Britain and Ireland

# The Pericardial Heart Valve

The Odyssey of a  
Continuously Evolving Concept

1971 - 2014



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Published by Society for Cardiothoracic Surgery in Great Britain and Ireland  
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1971 - 2014



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# Preface

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*In all enterprises, in any direction,  
what counts most of all is the first step*

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As the implantation of Pericardial Heart Valves proliferates across the world, the Society for Cardiothoracic Surgery in Great Britain and Ireland decided to take this opportunity to review the origin of this bioprosthesis and the results of its performance during the past four decades of clinical use. This description will facilitate the understanding of the qualities, the advantages and the successes, on the one hand, and the flaws and causes of failure of this valve on the other. Through such analysis, causes of events were understood and remedial measures taken, as necessary.

The SCTS is proud that the concept of 'man-made' tissue valves, the construction and the first clinical use of glutaraldehyde-treated, stent-mounted pericardial valves originated in Leeds, United Kingdom, in 1971, born out of the inventive, diligent and persistent work of Marian Ionescu. The experience over fifteen years with the use of some 200,000 first generation pericardial valves demonstrated - as established through the original concept - that the essential qualities of this valve could be preserved while making changes to eliminate the causes of valve failure.

This greatly significant initiative has opened the path for future development and modification of this versatile construction in response to clinical results. This was a magnificent journey from concept to widespread clinical practice with more than a million pericardial heart valves implanted worldwide to date. With the passage of time changes were made in valve construction, as required. A special change, derived from the original concept of 'man-made' valves, was the development of the transcatheter aortic valve implantation used in progressively larger number of patients.

Mr Marian Ionescu has provided an insightful knowledge of the stages of development of the pericardial heart valve; he dedicated a large part of his highly productive working life in Leeds to the development of these initiatives and to the follow-up of patients with pericardial valves.

The text continues by describing the importance of monitoring the clinical performance of these bioprostheses over time; the complications which occur and those which require further clarification; to appreciate the interaction of patient-related factors on the decision making process in the choice of heart valve prosthesis. The final chapter describes potential avenues regarding the future of cardiac valve surgery.

The SCTS would like to express its appreciation to Mr Marian Ionescu, whose work and inspiration are reflected in this publication. His life and hard work, imagination and daring may inspire younger heart surgeons and act as a stimulus to cardiac surgeons in future generations.

The SCTS wishes to express its deepest gratitude to the authors of the various chapters who gave of their unique expertise and precious time to make this publication possible. Thanks are also extended to Aaron Ramasinghe and Neil Howell for their collaboration. Isabelle Ferner has provided administrative help and support in her typical, efficient and organised manner, for which we are grateful.



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The Executive of the SCTS  
London 2014

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Chapter 1

# In The Beginning...

Conception, Construction and Clinical Use  
of the First Pericardial Valve

*Marian Ion Ionescu*

---

*“Tissue valves are the Utopia  
of mechanical prostheses”*

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Describing here the story of the pericardial heart valve can not start at the 'beginning'. Its beginning followed other beginnings as it happened with many other events before.

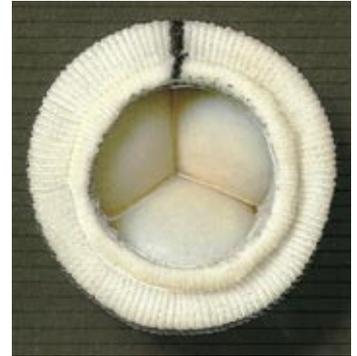
Most advances in surgery – as in all fields of human endeavour – in discovery and invention took place by progressive, stepwise achievements and only rarely in a chaotic burst of intense activity around a dream or an idea.

Open heart surgery was not an exception in this respect although during its continuous progress it had been the only surgical speciality to have paid the heaviest price on the way to success.

It is hard to single out one investigator or one discovery which has made this brave new world of heart valve surgery possible because the seemingly sudden eruption of brilliant exploits is due to decades of smouldering intellectual curiosity and the dormant torment of disinterested fools who died forgotten to save their successors the trouble of thinking.

However we can mention several recent landmark developments in the evolution of heart valve surgery.

It should be remembered that the stone age finished, not because they ran out of stones, but because they discovered something better, and this was later called 'evolution'.



*Pericardial Valve, Inflow View*

- 1957 - **Goeffrey Wooler** at the General Infirmary in Leeds was the first to devise a surgical technique for repairing incompetent mitral valves by annuloplasty<sup>1</sup>. He used it successfully in a series of patients despite the rather primitive conditions of extracorporeal circulation and the absence of intensive care facilities. His original method for mitral valve repair spread rapidly to other centres and other countries. This concept was adapted, improved, refined and popularised by others. In its present form it is used world-wide with great success.
- 1961- **Albert Starr and Lowell Edwards** in the U.S.A created and introduced in clinical practice the first mechanical valve<sup>2</sup> which was subjected, in time, to multiple modifications and was followed by the invention and use of a multitude of various types and models of mechanical valves. Their benefits, drawbacks and significant risks are well known and thoroughly documented.
- 1962 - **Donald Ross** in London introduced the use of aortic homografts into clinical practice<sup>3</sup> and, in 1967, the use of pulmonary autografts<sup>4</sup>. Following the use of free-hand insertion of these valves, it became apparent that stent-mounted animal tissue would represent a better solution for large volume manufacturing and easier insertion.
- 1965 - **Carlos Duran and Alf Gunning** in Oxford published the results of their experimental work of implanting porcine aortic valves in dogs<sup>5</sup>. The previous year they had already performed the first successful porcine aortic valve replacement in one human patient<sup>6</sup>.
- 1965 - **Jean Paul Binet** in Paris, France, began the use of porcine aortic valves for aortic valve replacement in humans<sup>7</sup>.
- 1967 - **Marian Ion Ionescu** in Leeds used, for the first time, in the mitral position in humans, porcine aortic valves mounted onto a Dacron cloth support and began a series of such valve replacements<sup>8</sup>.

- 1967 - **Hancock Laboratory** in Irvine, California, introduced the first commercially available stented porcine aortic valves for use in patients<sup>9</sup>. This was followed shortly thereafter by other American laboratories beginning to manufacture and commercialize such valves: Medtronic, Edwards and Shiley. Many surgeons and scientists contributed to the creation and improvement of the porcine valve.
- 1969 - **Marian Ion Ionescu** in Leeds created and started the clinical use of the stented autologous Fascia Lata heart valve<sup>10</sup>.
- 1969 - **Alain Carpentier** and co-workers in Paris, France, advocated the use of glutaraldehyde for the chemical treatment of porcine aortic valves<sup>11</sup>.
- 1971 - **Marian Ion Ionescu** in Leeds created a completely novel concept for constructing a new and different type of heart valve made of chemically treated bovine pericardium attached onto a support frame. He began the clinical use of this valve in April 1971<sup>12</sup>.

In 1976 Shiley Laboratory in Irvine, California, based on initial results obtained with the use of this new valve, began manufacturing and distributing this valve under the name “Ionescu-Shiley Pericardial Xenograft.”

The various progressive modifications made in the construction of this valve will be described later.

The essence of this novel concept is summarized as follows:

- The use of glutaraldehyde- treated bovine pericardium;
- The attachment of the pericardium onto a flexible Delrin stent;
- The technique of valve construction assured complete and synchronous movement of all three cusps allowing for a full orifice opening of the valve;
- The crucial and unique characteristic of this concept is that the valve being man-made, lends itself to a multitude of possible permutations of shape and configuration in order to progressively optimize its function. Due to this distinct and unique characteristic, the concept of the pericardial valve continues to persist and to be useful in various forms over a period of more than four decades of clinical use.

During the first 6 years of clinical use of the pericardial valve manufactured by Shiley, its advantages and negative aspects became apparent and had been documented, studied, evaluated and in part explained and remedied through the efforts of many research workers who found vital information in the experience with the ‘first generation’ of pericardial valves.



This led to the development and manufacture in the early 1980s of the ‘second generation’ of pericardial valves by several specialised laboratories. All these valves benefited, firstly, from the existence of, and the experience with, the Ionescu valves, and secondly, by using the principles of the initial Ionescu concept of pericardial valves which allows for a variety of modifications retaining the essentials: glutaraldehyde treated bovine pericardium attached onto a flexible stent. These improved ‘second generation’ valves, used almost exclusively in older patients (aged more than seventy years), and mainly for aortic valve replacement, have already shown their clinical benefit.

Since the first balloon-expandable transcatheter aortic valve implantation (TAVI) in 2002 by Cribier and colleagues<sup>13</sup> and the first self-expanding TAVI by Grube and his associates in 2004<sup>14</sup> this technique for aortic valve replacement using the principle of the pericardial valve concept has grown rapidly to more than 80,000 implants world-wide.<sup>15</sup>

## Realisation of the concept - Construction of the first valves

*The success of most things depends upon knowing how long it will take to succeed*

Charles Montesquieu de Secondat (1689-1755)

The leit-motif of Ionescu's continuous work on valve development was the dream, the idea to create a tissue heart valve which will endure and will not require long-term anticoagulation.

The creation of a prototype for the pericardial valve to be built began, in 1970, with a rod of lucite (plexiglass) which was sculpted with a dental drill into a mould for a 3-cusp valve Fig. 1. Simple empirical visual estimations were used to create, out of imagination, some shape that looked like an aortic valve (a man-made one) should look.

Papier-mache was used to mould a valve over the lucite form. (Probably Ionescu used the Guardian newspaper which explains the lack of conformity with the God-made valve). The next step was to make metal moulds which could be covered first with a water-soluble silicone over which a solution of polyurethane was applied. When this was set and dry some simple trimming was necessary to free the polyurethane 3-cusp valve from its mould. In a simple, primitive laboratory-built pulse duplicator several such valves were tested and proved to be competent. The apposition of the cusps was empirically established by simple adjustments to the top of the mould.



*Fig 1. Moulds for building the first experimental pericardial valves*

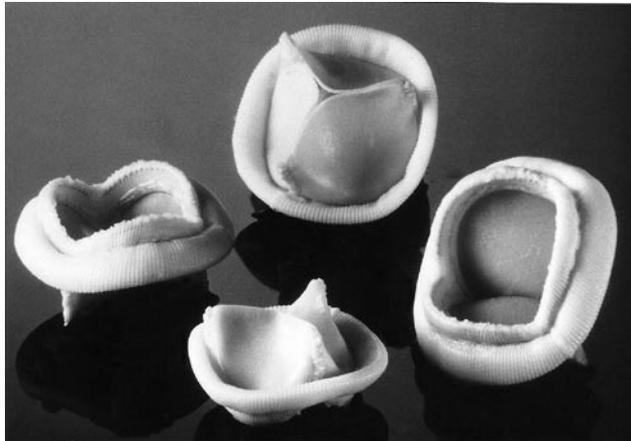
The movements of all three cusps was synchronous, their excursion complete and brisk, provided the thickness of the polyurethane for valve fabrication was correct. This thickness was obtained empirically depending on the cusps' movement and also by preventing air bubbles from developing inside the polyurethane solution. Ideal conditions for this were found by working in a cold chamber. This happened to be the butcher's refrigerator - the same butcher who also provided the bovine pericardial sacs.

Mr John Aylwin, a senior surgeon at the hospital in Leeds, who supported Ionescu in his unending experiments might have said that he saw some great things coming out of scruffy places!

From here the next step was to start the construction of the valve. Supporting stents were made in a small workshop in a village near Leeds, using a titanium alloy because of the lack of a more suitable material at that time. The prongs of the stent had, however, a certain amount of flexibility. These stents were covered with Dacron velour and the same material was used for the flange (the sewing rim) by Mrs Ionescu. The pericardial pieces, cut to size after treatment with glutaraldehyde, were attached on the outside of the stent and sutured at the base of the stent and to the top of the posts, initially around a small pledget of Dacron.

During 1970, simple pulse duplicator tests were carried out during conditions of continuous and pulsatile flow, with measurements of pressure gradients and speed of flow across the valves. These measurements, together with high-speed cinematography, showed excellent hydrodynamic function of these valves.

From the very beginning of this project of building a 'man-made' valve the material selected to be used was bovine pericardium. The main reasoning was that looking forward beyond the



*Fig 2. Family of Ionescu-Shiley Pericardial Valves.*

pig aortic valves seemed to be futile, therefore looking sideways was the answer - the bovine pericardium. This material possessed, grosso -modo, what at that time were considered some of the requirements of thickness, pliability, abundance and availability. The histological structure seemed acceptable as far as general architecture of the tissue is concerned.

With so little knowledge about this whole project, and few ways of finding out more, it was the moment to repeat Winston Churchill's saying: 'It is difficult to look further ahead than you can see'.

Between 1971 and 1976 the valves had been made in Ionescu's own hospital laboratory. Throughout these five years of usage in 212 patients, the performance of the pericardial valve in all three cardiac positions, was thoroughly evaluated. The results showed that this original valve exhibited the best haemodynamic performance, at rest and during exercise<sup>16</sup> when compared with the reported results of all other artificial valves in existence. It demonstrated a very low risk of embolisation even in the absence of long term anticoagulation treatment of the patients. There were no cases of valve thrombosis, intra-vascular haemolysis or sudden, unexpected valve failure. The durability of the valve was good at 5 years of follow-up<sup>17</sup>.

Based on these results, the Shiley Laboratory in Irvine, California, began to manufacture this valve and to distribute it worldwide under the name of the 'Ionescu - Shiley Pericardial Xenograft.' Fig.2

From 1976 onwards a series of modifications were made in order to improve the qualities and the performance of the pericardial xenograft. The selection and preparation of the bovine pericardium were standardised and rigorously controlled. For tissue fixation a solution of 0.5% purified glutaraldehyde was used. It contained an optimal proportion of monomers and polymers and an ideal cross-link density was obtained by controlling the concentration and the pH of the solution as well as its temperature and exposure time of the tissue to its action.

The highest quality of commercially available glutaraldehyde was purified at Shiley Scientific Inc. using a selective technique to control the glutaraldehyde monomer-polymer composition.

No single glutaraldehyde solution could either optimize the durability and flexibility of the tissue treated, or reduce its antigenicity and also provide the most effective degree of sterility. The importance and priority of each of the following parameters must be established and the most

appropriate balance reached in order to obtain the optimum quality of pericardium for valve construction:

- Glutaraldehyde concentration and composition
- pH and ionic strength
- Time and temperature of tissue exposure to glutaraldehyde
- The tissue configuration during the initial fixation.

All other procedures of tissue preservation claiming increased valve durability and patient survival are illusory unless scientifically documented.

The thickness and pliability of the pericardium were standardized and the direction of the macroscopically visible fibres matched for each three cusps of a particular valve. The supporting stent was changed. The titanium was replaced with machined Delrin which is an acetyl homopolymer with low 'creep' properties due to a stable molecular memory. It is flexible and shock absorbent, essential qualities for a tissue heart valve support. This new stent contained a radio-opaque marker at its base for easy identification. The contour of the scalloped posts was modified and the height of the stent reduced. The entire Delrin structure was covered with seamless Dacron velour and at a later stage, the margins of the scalloped edges were covered with a thin layer of pericardium in an attempt to prevent or reduce the abrasion of the leaflets when in contact with this margin during valve closure. The sewing rim was bolstered for better and safer attachment to the heart annuli and its shape was anatomically contoured into two different configurations to better fit in the aortic and the atrio-ventricular positions. Two other additions were made: an integral valve holder which prevented the touching of the valve's cusps, and a 'freeze-watch' indicator, attached to the outside of the containers of the valves, as a safe-guard against exposing the valves during transportation or storage at temperatures below 4 degrees Celsius.

The geometry of the valve was slightly modified due to changes in the shape of the stent and by removing the outside pledgets around the posts. This gave a more streamlined shape of the whole structure. These modifications had been progressively introduced and all of them were incorporated in the 'Ionescu - Shiley Low Profile Pericardial Xenograft' valve, which became available in 1983.

In order to remove any risk of pericardial leaflet abrasion Ionescu devised, in 1986, a new and completely different technique for attaching the pericardial leaflets to the stent. Shiley began implementing this idea by redesigning the stent. The new one was made of two wafer-thin, unequal, flexible Delrin components: an outside, standard shaped frame and an inner, smaller structure. The pericardial cusps were mounted inside the outer frame and were kept in position by the inner frame which was smaller and much thinner than the outer one. Through this arrangement, the lower parts of the pericardial cusps exit from the supporting frame at its bottom, and therefore the pericardium does not bend over the upper margin of the stent, eliminating the possibility of abrasion during the closure phase of the valve. As it was learned from clinical and from in-vitro studies, abrasion of the pericardium was a cause of valve failure when the tissue was attached on the outside of the stent<sup>(18,19)</sup>. The in-vitro testing of this modified pericardial valve showed almost identical hydrodynamic performance when compared with the existing pericardial valve.<sup>20</sup> Accelerated life-testing showed that failure of this new valve occurred some 3 to 4 times later than that of existing valves. When valve failure occurred it was not due to abrasion but through progressive fraying of the pericardium. Encouraged by these results, Shiley decided to start manufacturing this modified, improved valve called the 'Ionescu-Shiley Pericardial Optimograft'.<sup>21</sup>

At about that time grave problems were encountered by Shiley Laboratory with an increasing number of sudden failures of the Bjork-Shiley mechanical disc valve.<sup>22</sup> As a consequence of this unacceptable situation Pfizer, the giant drug manufacturer and owner of Shiley, stopped all manufacturing activities at Shiley Laboratory, with a view to liquidate the company. Consequently, not only the Bjork-Shiley valve (the culprit) was affected by this action, but all other products - valves, oxygenators, catheters, etc. - went out of production and the company was wound down.

At that crucial time for valve development, that decision was a blow to further work already under way for the final testing and evaluation of the new Ionescu-Shiley Pericardial Optimograft.

Approximately 200,000 pericardial valves manufactured by Shiley Laboratories were distributed around the world between 1976 and 1987 and it is presumed that most of them were implanted in patients.<sup>23</sup>

The use of this valve generated a lot of interest expressed in several specialist symposia, academic meetings, and numerous scientific articles published over the years.

The appropriation and organisation of this enormous material and the classification and interpretation of data has been a very difficult and complex task, especially because, contrary to what it is claimed, there remains a great deal of variation in standards of reporting in all essential chapters of a scientific work. In some cases it is quite impossible to follow such standards, as it will be described later. Despite all these difficulties and impediments, a general view of the performance of the pericardial valve as close to reality as possible could be obtained.

One should however keep in mind that any single investigator should resist the temptation to write a review of such a complex matter as tissue heart valves, and to cover the subject completely and fairly. One should also remember that when we study complex and variable conditions, averages must be rejected because they confuse while aiming to unify, and distort while aiming to simplify.

From the material available it is evident that the reported hospital mortality and, up to a certain point, late mortality are similar among the various publications of different authors, and do not directly reflect on the quality of the valve used.



## Haemodynamic Investigations and In-Vitro Testing of Valves

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*Truth is a torch which shines in the mist without dissipating it*

Claude Adrien Helvetius (1715-1771)

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The Ionescu pericardial valve had a large central opening almost equal with the inner surface area of the supporting stent. This, plus the pliability of the pericardial tissue, confer this valve exceptional hydraulic qualities. Haemodynamic studies by several authors<sup>16,24,25,26,27,28,29,30</sup>; investigating patients with pericardial valves, in both mitral and aortic positions, demonstrated that in all respects the haemodynamic function of this valve is superior to that reported for the porcine valves and, generally speaking, equal to that of the best mechanical prostheses. The haemodynamic results reported by other investigators are very similar to those by Tandon's group. Some authors stressed the advantage of very low pressure gradients across small pericardial valves (viz: 17, 19 and 21mm diameter) for implantation in small aortic roots without the need of complex surgical techniques for root enlargement.<sup>25,26,27</sup>

Tandon and associates<sup>28,29</sup> performed pre- and postoperative haemodynamic investigations at rest and during exercise in 110 patients. There were 51 with aortic valve replacement, 44 with mitral replacement, 3 with tricuspid and 12 who received multiple valve replacement. Following a technique and protocol developed at Leeds General Infirmary, from the group of 110 patients investigated, 13 patients with aortic and 6 with mitral valve replacement were subjected to multiple, sequential haemodynamic studies at rest and during exercise at the following intervals: aortic: preoperatively and at 9.9, 42.2 and 68.3 months postoperatively; mitral: preoperatively and at 11.2, 42.3 and 68.7 months postoperatively. The results obtained showed that the considerable improvement recorded at the first postoperative investigation was maintained up to 68 months following valve replacement<sup>16</sup> Fig 3A & B.

**Mitral Replacement Sequential Hemodynamic Data (mean ±S.E.M)**

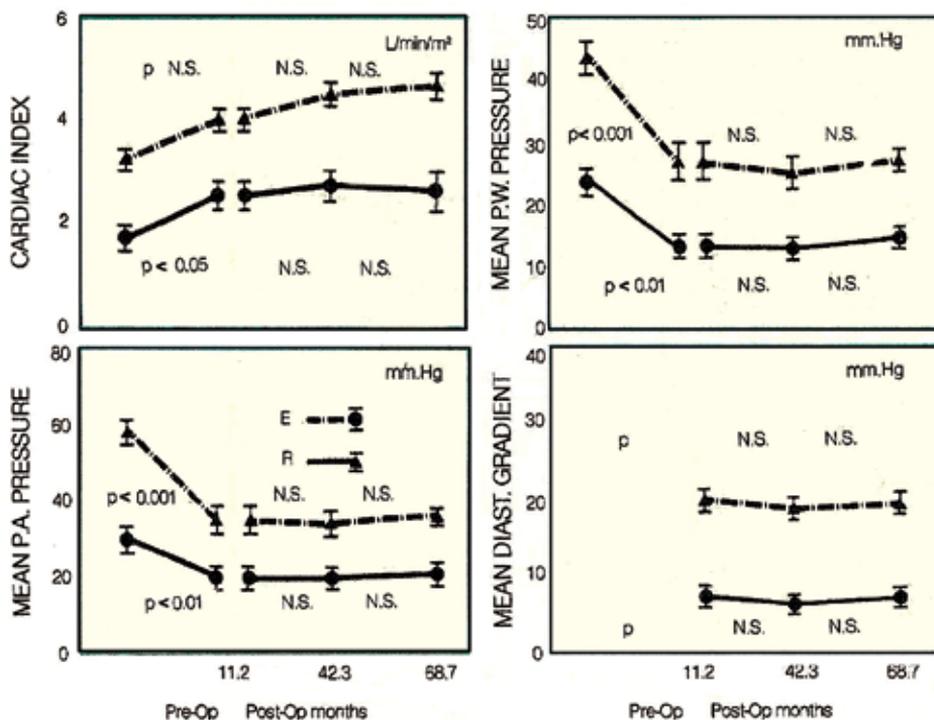


Fig3A. Graphic presentation of mean values at rest (R) and during exercise (E) of results from sequential haemodynamic investigations performed on six patients with mitral pericardial valve replacement.

In order to demonstrate visually the reasons for the great haemodynamic difference between the pericardial and porcine valves, Ionescu recorded in a 'pulse duplicator' the opening characteristics of two porcine valves (Hancock Modified Orifice and the recently modified Edwards valve) and two pericardial valves (the Standard and the Low-Profile Shiley valves).

All four valves were manufactured for clinical use and all had an implantation diameter of 25mm. The valves were tested under identical conditions in the mitral compartment of the pulse duplicator and photographs were taken at the peak of diastole. The flow rates were for each frame, from left to right: 0, 100, 200, 300 and 400 ml per second. The opening of the cusps of both types of pericardial valves is synchronous and regular, without three-dimensional flexure and the low-profile pericardial valve shows an even larger opening when compared with the standard pericardial valve.

Aortic Replacement Sequential Hemodynamic Data (mean ±S.E.M)

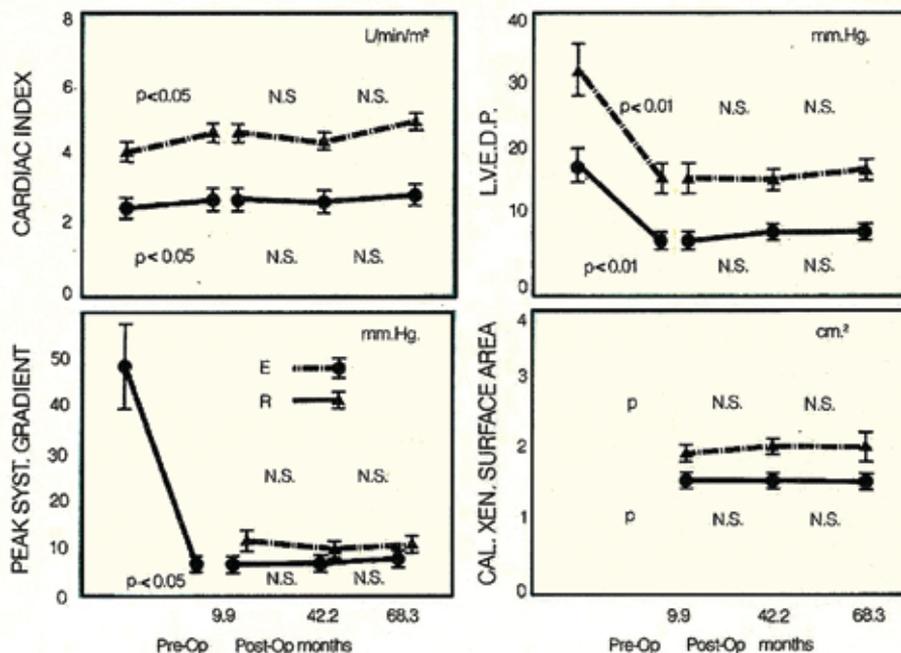


Fig3B. Graphic presentation of mean values at rest (R) and during exercise (E) of results from sequential haemodynamic investigations performed on thirteen patients with aortic pericardial valve replacement.

There are no crevices or dead spaces behind the open cusps of the pericardial valves. The difference between the porcine and the pericardial valves is clear in all respects Fig.4.

Many authors had studied, in-vitro, the hydrodynamic performance of the pericardial valve and found that it possesses better functional characteristics than the porcine valves and similar to those of the best mechanical prostheses.<sup>31,32,33</sup> In summary, the excellent haemodynamic function of the pericardial valve is one of its' great advantages and sets it aside from all other stented tissue valves.

An interesting observation was made by Rainer<sup>34</sup> during in vitro testing of tissue valves. At a flow rate of between 4.4 and 5.2 l/min, in a pulse duplicator set at 72-80 beats per minute, high-speed photographs were obtained. The valves tested were Hancock and Edwards porcine aortic valves and Ionescu-Shiley pericardial xenografts. Both porcine valves developed flutter and vibration in one of the three cusps, while the pericardial valve did not exhibit this anomaly. The author considers that tissue vibration is more destructive than any other mechanisms.

In addition to the usual description of hydrodynamic function of tissue valves, several investigators<sup>35,36</sup> tried to find answers to other aspects of valve function. It is almost universally mentioned in the specialised literature and in the publicity of manufacturers descriptions, the notion that tissue valves have to be mounted on a flexible stent. Wright<sup>37</sup> questions this assertion by explaining that making the inlet or the annulus section of the stent too flexible leads to valve distortion and insufficiency. Also it has not been scientifically demonstrated that annulus flexibility improves the clinical function or durability of valves.

The reason for the use of a flexible stent stems from an article by Reis and Hancock from 1971<sup>38</sup>. They reported a 90% decrease in mechanical stress on the porcine aortic valve cusps if

the commissures have no rigid attachment.

Thomson and Barratt-Boyes<sup>39</sup> have stated that this figure is too high since the tip of each frame-post deflects by only 0 - 0.21mm at a pressure of 100mmHg. Brewer et al<sup>40</sup> measured 1.2mm mean radial change of the aortic root wall in a pulse duplicator at a pressure of 120/80 mmHg.

Drury et al<sup>41</sup> demonstrated that :“There is a three dimensional movement of the commissural points within the natural aortic root and that at the present time there is insufficient data on which to make definitive recommendations regarding the ideal frame material and geometry. The resilient, flexible, creep and fatigue-resistant titanium alloy, together with the symmetrical design of the stent seems to present a logical step forward, but only long term clinical experience will confirm its significance.”

It is interesting to remember that Ionescu chose, for the first pericardial valves, to use titanium for stent construction for its lightweight and its flexibility characteristic. Fig.5

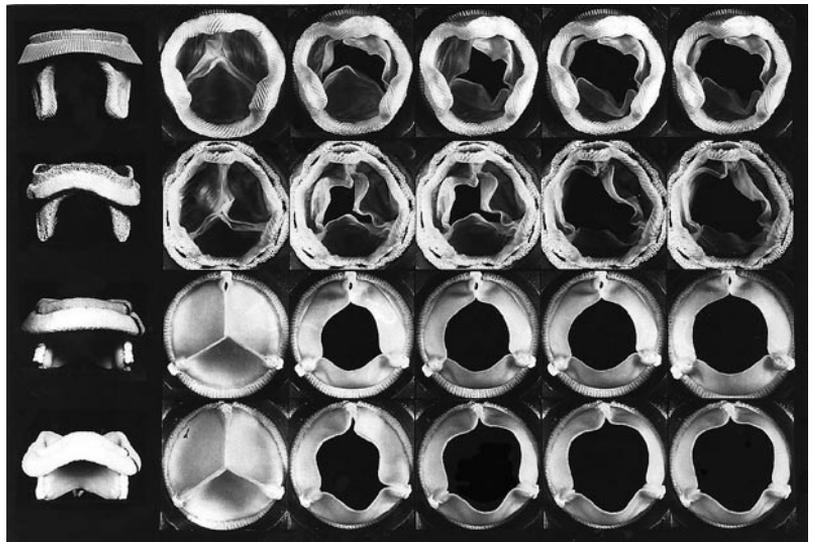
Clinical experience with bioprosthetic valves in many ways, exceeds design experience if true engineering, rather than empirical design procedures are considered.

The relevant information is scant in many respects and, as a consequence, valve construction has been empirical in nature with little understanding of the complex relationship between tissue properties, (following chemical treatment), the valve geometry (based on tri-leaflet design) and frame structure and flexibility and the flexibility distribution around the frame<sup>41</sup>

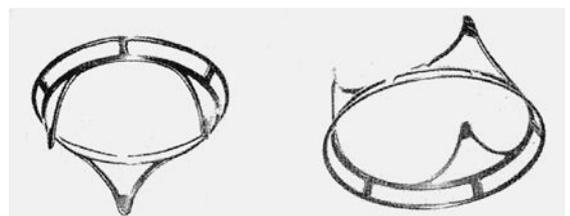
The creation by Ionescu of the first pericardial valve, in an empirical way, is certainly a good example of empirical design. It is worth mentioning that at the beginning of the use of flexible stents, the Hancock porcine valves suffered a series of failures due to the creep phenomenon until the qualities of plastic materials for stent fabrication became known.

Excessive flexibility of the Carpentier-Edwards mitral pericardial valve stent obliged the company to withdraw this valve from the market. It was reintroduced four years later following redesign of the support stent<sup>42</sup>.

Finally to paraphrase Thubrikar<sup>43</sup> one may say: Pericardial valves continue to emerge in a variety of designs with the aim that their performance will be improved. Since they



*Fig 4. Opening characteristics of porcine aortic and Shiley pericardial valves.*



*Fig 5. Valve frames made of titanium alloy with slightly flexible struts as originally used by Ionescu for the pericardial valves.*

have proven to be the preferred substitute for replacement of diseased heart valves in humans, the evolution of their design will continue until the ideal valve is found. This proves the veracity and the strength of the Ionescu Pericardial Valve Concept.

## Valve Related Complications

*Valves are like clocks, the worst is better than nothing, and the best ..... one could not expect them to function for ever.*

### Embolism, Thrombosis and Anticoagulation-related Haemorrhage

*It is what we believe we already know that prevents us from learning*

Claude Bernard (1813-1878)

While dealing with a very large number of reports from different hospitals with various numbers of patients who received pericardial valves and were followed-up for differing durations of time, from 5 to 10 years, and especially because the reporting did not follow an ‘established’ albeit loose ‘standard’ of identification, description and grading of the events, it was decided to enumerate the results from some of the more representative series reported and draw only general conclusions - Table 1.

The following data shows the results as given in actuarial percentages of freedom from embolism.

*Table 1. Freedom from Embolism*

Main Author	No of Patients	Duration Follow-up	Actuarial freedom from embolisation
DA Cooley <sup>44</sup>	2701	5 years	93.2% for all patients. 96.1% for aortic, 89.7% for mitral and 94% for mitral and aortic replacement
A Pavie <sup>24</sup>	675	5 years	95.8% for all patients
M Holden <sup>45</sup>	290	6 years	5 Emboli (1 certain, 4 doubtful). 0.70% per patient year
JM Revuelta <sup>26</sup>	80	8 years	93.6% for all patients
Gonzales-Lavin <sup>46</sup>	224	8 years	95.3% for aortic, 97.4% for mitral replacement 4(46 (43 )
JB Garcia-Bengochea <sup>25</sup>	248	8 years	97.5% for all patients
NP Silverton <sup>(47,48)</sup>	492	6-10 years	96.8% for mitral, 97.2% for multiple replacements
XD Zhu <sup>49</sup>	520	9 years	95.8% for all patients
MI Ionescu <sup>17</sup>	1171	10 years	96.4% for aortic, 96.8% for mitral, 97.2% for multiple replacements

It is interesting to note that the actuarially presented results of freedom from embolism improve in a direct proportion with the length of the follow-up.

From perusing innumerable publications on the results of heart valve replacement with pericardial valves, concerning the rate of embolic complications, one may formulate several conclusions.

A clear picture concerning the exactitude of thrombotic and embolic complications of artificial heart valves, and especially of pericardial valves, seems to be very difficult. Our knowledge at present is superficial and incomplete concerning the real causes and the risk and contributing factors to this complex phenomenon. Consequently, it has never been practical to try to standardise definitions, and even more complicated to establish lines of treatment. Everyone talks of 'causes' and 'risk factors' but no-one possesses any scientific evidence to this effect.

The so-called 'risk factors' for embolisation, with the exception of atrial fibrillation, can be called, at best, 'scientific illusions'. Consequently, any scientific, logical way of establishing a therapeutic means for preventing such phenomena due to unknown or incompletely understood causes is doomed to remain empirical, and the end results uncertain.<sup>25,46,48,50</sup> There are miriads of reports for and against anticoagulant treatment for patients with tissue heart valve replacement. In addition, heart valve replacement patients are followed-up by a 'committee' made up successively by the surgeon, the cardiologist, the general practitioner in this or another town, etc., etc. The impression of knowledge or our acceptance of ignorance compound this matter further. Our only salvation - the patients and our own - would be an artificial heart valve which carries a very low risk of embolism, and therefore would not require, in the majority of cases, anticoagulant treatment.

One main draw-back in the recent 'scientific' literature on pericardial valves is the fact that the essential data for arriving at an intelligent interpretation of results is missing. There is no description of the pre-operative condition of the patients concerning cardiac rhythm, various arrhythmias, atrial fibrillation, anticoagulant treatment, previous systemic emboli, etc., etc., and scant information about the post-operative condition: cardiac rhythm, the nature and duration of anticoagulation, the time of occurrence of embolic phenomena and the magnitude and sequelae, if any.

All this is already in the past now, for practical purposes, one can conclude that the pericardial valve carries a very small risk of embolisation, much smaller than that of the porcine valves even in the absence of anticoagulant treatment. The risk of pericardial valve thrombosis is exceedingly remote. The extremely few cases reported have not been thoroughly investigated as far as the timing of occurrence, the cause or the contributing factors, related or not to the valve, are concerned. Anticoagulant related haemorrhage was very rarely reported because few patients received prothrombin depressants for long periods of time (*Sublata Causa Tollitur Effectus*).

There are a few reports about patients with tissue valves in the mitral position and with atrial fibrillation. Half of the patients were anticoagulated and the other half were not. However there was no difference in the embolic rate between patients with anticoagulants and those who were not anticoagulated<sup>51,52</sup>. In addition, it was observed that the rate of embolisation appears to be decreasing with the passage of time with the pericardial valves, unlike the experience with porcine valves in the mitral position where the risk remained constant during the whole period of follow-up in spite of different schemes of long-term anticoagulation.<sup>48</sup>

The favourable embolic rate and virtual lack of valve thrombosis of the pericardial valve appear to be due to the quality of the tissue, and especially to the design of the valve with a smooth and synchronous movement of all three cusps and the streamlined structure conferring the valve optimal haemodynamic characteristics even at low flow rates.<sup>32,46,48</sup>

Following the description of embolic complications surrounding the use of pericardial valves, it is important to discuss two essential points of this phenomenon.

The first one is the persisting but erroneous usage of the term 'thrombo-embolism' repeated ad nauseam in most publications and oral presentations.

Many investigators describing the clinical performance of artificial heart valves use the term 'thrombo-embolism' for what in reality are two distinct phenomena: thrombotic obstruction of the valve and systemic emboli or embolism. Thrombosis is a clotting event which occurs 'in situ', while emboli, of various sizes and differing composition and origins, are circulating particles which almost always reach the end of their journey in a branch of the arterial tree.

Nashef and his associates<sup>53</sup> consider that in the context of heart valve replacement, systemic embolism may appear to be unrelated to the type of artificial valve in situ, while thrombotic obstruction is directly related to the valve type. He also demonstrated that patients who develop thrombotic valve obstruction were not at a higher risk of systemic embolism than others. The analysis of Nashef shows that these two complications have markedly different incidence patterns.

This matter of nomenclature had been raised several times in the past by different authors but, surprisingly, unsuccessfully.<sup>53,54</sup>

The second aspect of this matter is to try to clarify the complex phenomena of thrombosis and embolism in the context of heart valve replacement, especially with tissue valves.

At present it is impossible to determine with certainty whether all episodes considered to be embolic events are due to the migration of particles from an intracardiac thrombus. There is however some evidence that this may not be the case.

In a progressively aging population undergoing open-heart surgery such events could result from other causes than heart valve replacement. The commonly described causal factors are: atheromatous disease, sometimes calcification of the ascending aorta, the carotid arteries and the cerebral branches of the carotid and vertebral arteries. In addition, hyperlipidaemia, blood hypercoagulability and polycythemia vera had been implicated, mainly in the context of strokes. During open-heart procedures other causes for embolism may exist, such as: various particles of foreign material from the removal of calcified cardiac valves, flakes of dried blood from surgical instruments and even microscopic loose particles of cut sutures. Rare causes could also be considered like the paradoxical embolus through a patent foramen ovalae or an atrial septal defect.

It is surprising that when describing embolic episodes following tissue heart valve - or any other type of valve replacement for that matter, the factor 'stroke' has not been considered, especially when dealing with patients aged beyond 70 years.

There is a very significant incidence of 'naturally occurring' strokes in the population.

Barratt-Boyes<sup>55</sup> drew attention to this situation explaining that the older the patients become for valve replacement, the more important this factor is. Because of this background of stroke in the population operated upon, he refuses to list as embolism such events in his publications on homograft aortic valve replacement although the incidence is recorded.

In the United Kingdom during the last three years there were approximately 150,000 strokes per annum (one every five minutes), causing, in 2010, about 50,000 deaths. In England the incidence is between 2.2 to 2.4% per 100,000 of population per annum, with similar figures for Northern Ireland and Wales, while in Scotland the rate was higher at 2.5 - 3.3%. It is also known that 85% of strokes are ischaemic in origin. In this group the cause is atherosclerosis in 50% of cases, lacunar strokes in 25%, cardiac in 20% and the rest are produced by conditions of rare or obscure origin. Of course there is considerable variation according to age with heavier prevalence in the 65 - 95 years old age group. World-wide there are 15 million strokes every year<sup>56</sup>.

The fact that the age of the population requiring aortic valve replacement advances progressively, the 'factor stroke' becomes more important in the interpretation and reporting of the cause and the nature of embolic complications. The known incidence of stroke in the elderly population represents a certain part of the reported embolic rate following aortic valve replacement with tissue valves.

Another element to be taken into account when describing the survival and the embolic rate of patients older than 70 years is the life-span of this population.

Leguerier and his colleagues<sup>57</sup> compared the survival rate of patients having aortic valve replacement with the death rate of the general population of the same age (as established by the French National Institute of Statistics - INSE) and found them quite similar). The actuarial survival curves showed at 5 years 84.3% for the general population and 67.2% for patients with aortic valve replacement (operative death of 10.1% included). At 8 years the figures were 65% and 56% respectively.

Ignoring this reality, several definitions for symptoms of systemic embolism were artificially created and published over the years, some of them touching the absurd and some others built on imagination. They did a lot of damage to the reporting of these complex and poorly understood phenomena. As an extreme example, one may quote: the person who experienced dizzy spells or had not remembered in time the name of the seventh king of ancient Rome remained a peaceful law-abiding citizen unless he had an aortic valve replacement, then these events will be classified as embolic episodes! This example calls for a clear differentiation between 'soft' and 'hard' symptoms of cerebral vascular accidents.



The exact incidence of systemic embolism generated by heart valve replacement in general, and by each type of tissue valve in particular, when considered in the context of the 'stroke factor' which itself is responsible for about 2.3% per annum (in England) of cerebral vascular accidents in the general population, is extremely difficult to ascertain. This probably is the cause of different figures of embolic rates published by various authors about series of patients of differing age groups.

In patients requiring medical or surgical treatment for mitral valve disease the problem is, in principle, the same as for those with aortic valve replacement, although it becomes more complicated because mitral valves - diseased or repaired / replaced - function in a different environment between two heart chambers and therefore are exposed to considerably different pressure regimes when compared to the aortic valve environment. In addition, the age of the patients in this situation is much lower than that of patients with aortic valve replacement.

In order to better understand the complex nature of embolism in patients with mitral valve disease a retrospective analysis of data published over the years on this subject may shed some light on the pathophysiology on this complication.

The association of systemic embolism with chronic rheumatic mitral valve disease has been recognised for many years.

Table 2<sup>47</sup> lists the approximate incidence of systemic emboli in several large and well reported series of medically treated patients with chronic rheumatic mitral valve disease. The incidence of systemic embolism of 1.5 to 3.7 episodes per 100 patient years seems to have been reduced by the use of anticoagulation. It must be stressed that the enthusiasm for anticoagulant prophylaxis derived from a study in Norway initially in only 17 patients all of whom had previously experienced recurrent documented emboli and who acted as their own control. A second study comprised 15 patients anticoagulated after their first embolic episode, for a mean period of 6 years, with 17 control patients.

The particularly strong association of embolic phenomena with chronic atrial fibrillation is apparent in almost every reported series, but as shown in Table 3<sup>47</sup>, there is no significant correlation between embolism and any other factor previously considered to be associated with an increased embolic risk.

With the advent of closed mitral valvotomy it became apparent that amongst the benefits derived from the relief of mitral stenosis was a reduction in the incidence of systemic emboli following this operation.

Table2: Embolic complications in Medically Treated Patients with Rheumatic Mitral Valve Disease<sup>47</sup>

Sources	No of Patients	Follow-up years max mean		Emboli % per Annum
Without Anticoagulation				
Rowe et al	250	10	--	2.0
Szekely	754	22	7.7	1.5
Coulshed et al	166	16	3.9	3.7
With Formal Anticoagulation				
Flemming	217	up to 9 years		0.8

Table 3: Factors Considered to be Related to Systemic Embolism in Patients with Mitral Valve Disease

Authors and treatment	No of patients	History of embolism	Age	AF	NYHA Class	CTR (LA size)	Clot in LA/LAA	Calcified valve
Coulshed et al Medical treatment	839	N/A	+	+	+	--	--	--
Flemming Medical treatment	500	N/A	+	+	--	--	--	--
Ellis and Harken CMV	1500	?	--	+	--	--	--	--
Vega et al OMC	159	?	--	+	--	--	?	--
Borkon et al MVR (Hancock)	62	--	--	+	--	--	--	--
Hill et al MVR(Hancock)	124	--	--	+	--	--	--	--
Lakier et al MVR (Hancock)	125	--	--	+	--	?	--	--
Cohn et al MVR (Hancock)	80	--	--	+	--	?	--	--
Silverton et al MVR (Pericardium)	400	--	--	+	--	--	--	--

AF - atrial fibrillation, NYHA - New York Heart Association, CTR-Cardiothoracic ratio, LA - left atrium, LAA - left atrial appendage, N/A - not-applicable, MVR - mitral valve replacement, OMC - Open mitral commissurotomy, Hancock - Hancock porcine valve, Pericardium - pericardial xenograft valve, ? - not clarified.

Table 4<sup>47</sup> shows data from six reported series: two following closed mitral valvotomy, three more recent series describing the survivors of open mitral commissurotomy and one series following mitral annuloplasty. Although there is a variation in the number of patients receiving long-term anticoagulation there is a striking similarity in the low rates of systemic embolism following such conservative procedures. One may speculate that the slightly higher embolic rate in the series followed up for a longer duration, (15 - 20 years) may be due to the progressively less efficient mitral valve caused by restenosis and also, presumably, with the increasing incidence of atrial fibrillation.

It is against the background of this data that we should consider the embolic risk of tissue heart valve substitutes.

*Table 4: Embolic Complications Following Conservative Rheumatic Mitral Valve Operations<sup>47</sup>*

Source	No of patients	Atrial Fibrillation %	Follow up max yrs	Follow up mean yrs	Operation	Anti-coagulation treatment	Emboli% per annum
Ellis and Harken	1590	51.6	11.0	6.0	CMV	None	0.46
Ellis et al	913	?	15-20	-	CMV	?	1.1
Haseth et al	191	28.8	10.0	4.5	OMC	14	0.56
Gross et al	197	common	10.1	3.5	OMC	20.3	0.34
Vega et al	159	40.0	5.3	3.0	OMC and or MR	?	0.61
Tandon et al	115	72.5	19.0	9.0	MR	20	0.61

*CMV - Closed mitral valvotomy, OMC - Open mitral commissurotomy, MR - Mitral repair*

Tables 5 and 6<sup>47</sup> present in a similar manner to previous tables, the reported incidence of embolism in patients with tissue valves in the mitral position. With the exception of the Leeds series at the foot of Table 6, all these series used porcine xenografts for mitral valve replacement. Different groups have used differing criteria for long-term anticoagulation, but despite these therapeutic differences, there is an uncanny similarity in the reported incidence of embolism. The incidence of approximately 3 episodes per 100 patient years was considerably greater than that seen after conservative mitral valve operations and than that reported in the Leeds series and seems unaffected by the different proportions of patients anticoagulated. Whilst patients receiving tissue valves substitute have a similar surgical approach and a similar profile of diseases and of disease severity, the only difference lies in the nature of valve substitute. The construction and haemodynamic performance of the pericardial xenograft is known to be much different from the porcine aortic valves<sup>16,31,32,33</sup>. The incomplete and sequential opening of the leaflets of porcine valves may have some bearing on their propensity for embolisation and valve thrombosis.

Table 5: Embolism in patients having Mitral Valve Replacements with Hancock Porcine Valves<sup>47</sup>

Institution	Years of Valve range	No. of patients	Emboli % per annum	Long term anticoagulation
Kansas University	1970-75	104	4.8	If LA thrombus
Henry Ford Hospital	1971-75	228	4.7	54% of patients
Henry Ford Hospital	1971-75	125	2.9	75% of patients
Stanford University	1971-75	243	5.2	15% of patients
Stanford University	1971-78	561	3.1	31% of patients
Brigham Hospital	1972-77	131	3.8	If AF or large LA

LA- left atriem, AF- atrial fibrillation

Table 6: Embolism in patients having Mitral Valve Replacement with tissue valves<sup>47</sup>

Institution	Valve	Years of valve usage	No. of patients	Emboli % per annum	Long term anticoagulation
Pacific Medical Center	Hancock	1974-77	126	5.3	50% of patients
Pacific Medical Center	Hancock	1974-79	124	3.12	62% of patients
Pacific Medical Center	Hancock	1974-78	72	3.16	100% of patients
British Columbia University	Carpentier Edwards	1975-78	261	3.5	45% of patients
N.I.H Bethesda	Hancock	1970-75	62	3.3	6.5% of patients
Good Samaritan Hospital	Angell-Shiley	1975-80	103	3.4	If AF, history of T/E, LA thrombus, giant LA, intimal disruption
Leeds University	Ionescu-Shiley	1971-82	400	0.67*	NONE

AF- atrial fibrillation, T/E- thromboembolism, LA- left atrium, N.I.H- National Institutes of Health

\* Similar low incidences of embolic events in patients with pericardial valve replacements were reported and presented in actuarial form by numerous authors<sup>17,24,25,26,44,45,46,47,48,49</sup>

The final element of risk in the equation lies in the use of long-term anti coagulation, mainly warfarin sodium. Table 7<sup>47</sup> summarises the reported incidence of severe and fatal haemorrhage associated with this therapeutic regimen.

Table 7: Serious and Fatal Bleeding Complications in Patients with Mitral Valve Disease Treated with Anticoagulants<sup>47</sup>

Sources	Year of publication	No of patients	Follow-up max years	Follow-up mean years	Treatment	Bleeding % per annum
Flemming and Bailey	1971	217	9	--	Medical	2.3
Gross et al	1981	40	10.1	3.5	Open mitral valvotomy	0.79
Hill et al	1982	72	--	2.2	Mitral Hancock	6.32
Angell et al	1982	103	5	--	Mitral Angell-Shiley	2.1
Borkon et al	1981	32	10	5.4	Mitral Hancock. Aortic Starr	4.9
Bjork and Henze	1979	413	10	4.8	Mitral Bjork-Shiley	6.3
Edmunds (collective review)	1982	21	550 patient years from 9 reports		Various mitral prostheses	0.5-6.3 (2.19)
Oelert et al (ref)	1982	42	4	19.6 mths	Mitral and aortic Pericardial	8 episodes (2 severe)

In view of this risk of bleeding and also encouraged by the low incidence of embolism in patients undergoing mitral and multiple valve replacement, several authors have decided not to routinely use long term anticoagulation in patients with pericardial valve replacement<sup>25,45,46,47,58</sup>. It is also reported that most of the small number of embolic episodes following mitral valve replacement with pericardial xenografts occurred during the first six postoperative weeks<sup>48,58</sup>.

The very low risk of embolisation, the virtual absence of thrombotic obstruction of the pericardial valve and the published evidence that systemic embolisation still occurred in patients treated with anticoagulants<sup>(59,60)</sup>, justifies the decision, not to use prothrombin depressants beyond the six postoperative weeks in these patients.

## Infective Endocarditis

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*Ignorance is the curse of God, knowledge the wing wherewith we fly to heaven*

Shakespeare (1564-1616) Henry VI Part 2, Act IV

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Infective endocarditis is a severe condition which occurs on native as well as on artificial valves. Both mechanical prosthetic devices and tissue heart valves are affected. The incidence of endocarditis, in western countries, ranges from 1.5 to 6.2 cases per 100,000 people per annum. The cumulative rate

of prosthetic valve endocarditis is 1.5 to 3.0% at one year following valve replacement and 3 to 6% at 5 years, the risk being the greatest during the first six months after valve replacement.

Prosthetic valve endocarditis arising within 2 months of valve surgery is generally the result of intra-operative contamination of the prosthesis or a bacteraemic post operative complication. The nosocomial nature of these infections is reflected in their primary microbial causes: coagulase-negative staphylococci, S. Aureus, facultative gram negative bacilli, diphtheroids and fungi. Epidemiologic evidence suggests that prosthetic valve endocarditis due to coagulase negative staphylococci that presents between 2 and 12 months after surgery is often nosocomial in origin but with a delayed onset.<sup>61</sup>

This short introduction may help to reflect on the various and sometimes opposing view-points concerning the ‘origin’ of prosthetic valve endocarditis. As in most recent scientific reports, some descriptions of tissue valve endocarditis suffer from the same lack of clarity and standardization in the presentation of facts and do not give all relevant details for a better understanding of events and their causes. From eight published articles of large series of patients with Ionescu-Shiley Pericardial valves, only one report presents a higher than average incidence of valvular bacterial infections.<sup>59</sup> The other seven publications describe the rate of infection with figures of similar magnitude, as shown in Table 8.

Table 8. Freedom from Infective Endocarditis

Main Author	No of patients	Duration of follow-up yrs	Linearized rate of infection	Actuarial freedom from Infective Endocarditis
Pavie <sup>24</sup>	675	5		98.2% for all patients, 97.8% for aortic, 99% for mitral, 100% for multiple valve replacements
Duncan <sup>62</sup> (A)	2720	6		97.3% for all patients, 97.4% for aortic, 97.6% for mitral, 96.3% for multiple valve replacements
Ionescu <sup>17</sup> (B)	1171	10		93.7% for all Patients, 94.7% for aortic, 97.1% for mitral, 89.3% for multiple valve replacements
Zhu <sup>49</sup>	520	10		98% for all patients
Revuelta <sup>26</sup>	239	8	0.67% per patient year	
Garcia <sup>25</sup> Bengochea	248	8	0.78% per patient year	
Holden <sup>45</sup> (C)	290	6	1.1% per patient year	
Bachet <sup>59</sup> (D)	224	6	1.6% per patient year	

Footnotes to the table:

(A): The authors make an interesting remark. Prior to heart valve replacement 86 patients suffered from infective endocarditis but only 9 of these patients developed recurrent infection following pericardial valve replacement.

- (B): *It is of interest to note that of the 17 cases of infection, 15 occurred between 1976 and 1981 and only 2 cases between 1981 and 1985. Ionescu's group took draconian measures in trying to jugulate post-operative infections which they considered to be, in great part, nosocomial in origin. Those measures were directed at systematic pre-operative dental examination and treatment, search for any hidden, potential foci of infection - urological, upper and lower respiratory tract, judicious selection of antibiotic cover of the patient before, during and following heart valve replacement operations and strict monitoring of all signs of infection in the post-operative period. It appears that these measures were successful.*
- (C): *On two occasions Holden implanted, successfully, pericardial valves in patients with infective endocarditis and he even advocated the use of such valves in similar situations because some considered the pericardial valves to be more resistant to infection than other devices.<sup>45</sup>*
- (D): *This group considered that in their hands the pericardial valves were more prone to infection than the porcine valves, and also when compared to the results with pericardial valves published by other surgeons.*

In conclusion, it is obvious that the risk of infective endocarditis in pericardial valves is not dissimilar from that encountered in porcine valves at least up to 10 years after valve insertion. It can also be considered that the minor variations occurring in the published reports are due to local hospital differences, surgical technique, general handling of the valves and other factors.

One rarely finds a patient who was treated medically for proven endocarditis on his own valve who does not require valve replacement sooner or later.

There is no fundamental reason why any pericardial valve should become infected more frequently than another one except if the patient becomes septicaemic and the infecting organisms will reach the valve area. It appears illogical to claim that because one surgeon reported a higher incidence of infective endocarditis with one type of valve, that there could be any significant differences between 'his' valves and those implanted by other surgeons. The difference is in the number of patients with circulating infecting micro-organisms capable of infecting the valve area.

Most authors do not consider infective endocarditis as a valve related failure and do not include cases of infection in such statistics. The pericardial valve does not behave in a different way from other tissue valves as far as infection is concerned, with probably one exception. In the impression of some surgeons, the pericardium itself may be more resistant to infection than the porcine valve.

## Structural Valve Dysfunction

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*In the incense burner, smoke and perfume are inseparable*

Hindu saying

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The durability of the pericardial valve, like that of all other artificial heart valves, depends on multiple factors, one of the most important being the environment in which the artificial valves function. Structural valve dysfunction (SVD) occurred with pericardial valves and it has been reported in several publications. Unfortunately, many reports do not contain some of the essential data and details necessary for building a clear image of this crucial aspect of valve performance. Table 9 tabulates some of the available data on primary tissue failure.

Table 9 Structural Valve Dysfunction

Main Author	No of patients	Follow-up years	No of valves with structural dysfunction	Free from SVD. Actuarial
Pavie <sup>24</sup> (A)	675	5	2 Aortic, Calcified and Fibrosed	99;1% All patients
Revuelta <sup>26</sup>	90 Aortic	8	2 valves Calcified(0.71% per patient year	89.9%
Gonzales-Lavin <sup>58</sup>	240 Aortic	8	12 Valves, 11 Calcified	88.4% Aortics only
Garcia- <sup>25</sup> Bengochea	248	8	2 Valves (0.22% per patient year)	
Duncan <sup>62</sup> (B)	2720	6	77 Valves, 52 Calcified, 25 Tears	91.5% Mitral, 86.2% Mitral and Aortic, 84.5% Aortic
Bachet <sup>59</sup>	224	6	5 Valves, 4 Tears, 1 Calcifies (0.80% per patient year)	
Van Sweiter <sup>(63)</sup>	444	6	2 Valves, Tears, (0.20% per patient year)	
Zhu <sup>49</sup> (C )	520	9	5 Valves	92.1% mitral, 89.9% Aortic
Ionescu <sup>17</sup>	1171	9-10	25 Valves,15 Tears, 9 Calcified, 1 fibrosed (Mitral 0.72%, Aortic 0.94% per patient year)	88.7% Mitral, 86.9% Aortic
Keon <sup>64</sup>	637	8	19 Valves,, 15 Tears, 4 Calcified	89% Mitral, 87% Aortic
Kawazoe <sup>65</sup>	319	7	4 Valves, 3 Mitral, 1 Mitral and Aortic (all cusp tears)	93.4% mitral, 90.5% Aortic
Nistal <sup>66</sup> (D)	133 Aortic	7	8 valves All calcified, 2 with additional tears	80% All Valves
Moran <sup>67</sup>	400	5	9 Valves (8 Mitral,1 Aortic) 4 Calcified - mean age 37.5, Tears - mean age 50.2 (0.87% per patient year)	

Remarks for structural valve dysfunction

(A): The age of the patients ranges from 8 to 90 years (mean 57). 74% were over 70 years of age. The age of the 2 patients with valve failure (calcification) was not mentioned.

(B): The most important element in this large series is the demonstration that one of the most important factors in valve calcification is the age of the patient at the time of valve implantation.

(C): In this series, the authors mention, in addition, 4 cases of entanglement of sutures around the struts. These 4 patients were re-operated upon at between one week and 50 months following the first valve operation.

(D): *The authors stated that all 8 failures were due to valve calcification and that 2 of them had additional tears. They find that their results with 'calcification' in all failed valves are contrary to Gabbay's results<sup>18</sup> where failures occurred mainly through cusp tears.*

This table is only an attempt to give a general impression and to provide a basis for a more detailed interpretation of results. However, several conclusions can be formulated on the complex, varied, and in some cases controversial results published. As very often, a good amount of significant data is missing and this complicates the task of being precise and fair in interpreting the results.

It appears that the great majority of pericardial valves function correctly until about 6 to 7 years post-implantation. Beyond 7 years of follow-up the actuarial figures for freedom from valve failure start to decrease. In the table, the risk of valve failure seems to be greater in the aortic position as reported by some authors. In reality, the general consensus among surgeons, in various presentations and formal discussions and the evolution in time shows the contrary.

The durability of these pericardial valves varied, in general, from 5 to 27 years.

The great majority of valves in the mitral position began to deteriorate from 5 years post-implantation and this process increased even faster after 10 years.

The valves in the aortic position fared much better. At 10 years and beyond, the valves did function well, as reported by various authors<sup>69,70</sup>. The deterioration through calcification and cusp tears advanced progressively from 12 years post-implantation.

There were, however, many valves that functioned correctly between 12 and 17 years. Ravichandran<sup>69</sup> reported a series of 34 patients (with 41 valves) which were operated upon for removal of Ionescu-Shiley pericardial valves. The failure of these valves occurred at a mean post-operative duration of 11.3 years (range 5 to 17 years). There were 30 mitral and 11 aortic valves involved and the majority were heavily calcified.

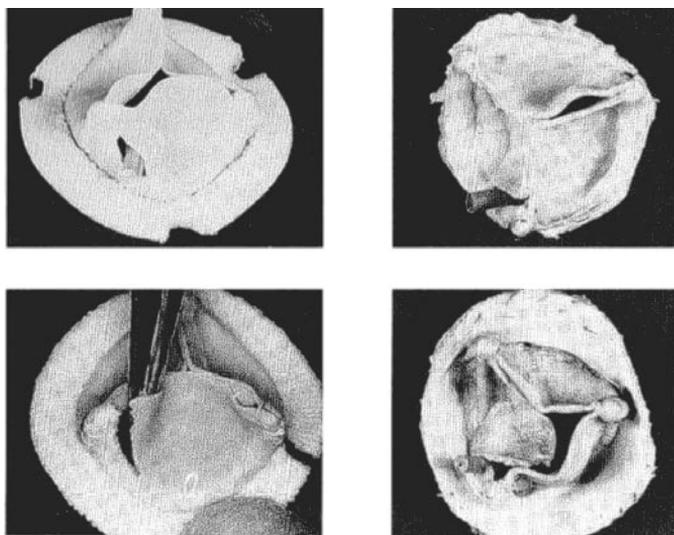
Exceptionally, 7 Ionescu-Shiley pericardial valves were reported to have been removed between 21 and 27 years post implantation<sup>71,72,73,74,75,76</sup>. Whether more such late events occurred and went unreported remains purely speculative.

There were 4 valves from the aortic position, 2 from the mitral and one each from a patient with mitral and tricuspid replacement. Only two reports mentioned the age of the patients at the time of implantation (37 and 49 years).

The pathology findings, very similar for all these seven valves, showed general stiffening due to diffuse calcification of the cusps but none of them had cusp tears. The most striking finding in all these valves was the presence of pannus formation by connective tissue growing over the upper margin of the stent - without any doubt - preventing the abrasion of the pericardial tissue and allowing, therefore, the valves to function for durations beyond any expectations.<sup>76</sup> The pannus grew exactly over the useful area of the Dacron covered stent, but only on that part without encroaching on the cusp tissue. It padded in a 'natural' way the abrasive part of the stent.

This finding may have great significance concerning valve durability. It may help to understand the causes of pannus formation in this particular situation and also the causes and mechanisms which help to delay or even to prevent early calcification of pericardial valves. Knowing that all the pericardial valves described here came from the same manufacturer, it seems logical to question the participation of the host in this phenomenon.

The known modes of tissue valve failure are: tearing of the pericardium, calcification of the valve and, exceptionally, fibrosis of the cusps. Tears represent approximately 25% and calcification 75% of



*Fig. 6. Comparison of abrasion lesions in pericardial valves in the 'life tester' (left side) and valves removed from patients (right side). The upper row shows an abrasion lesion which occurred at around 8 o'clock (left) and a similar lesion around 4 o'clock in a valve explanted from the aortic position at 76 months after implantation (right). The lower row shows the abrasion tear which extended to the free margin of the cusp (left) and a similar lesion in a valve explanted from the mitral position at 89 months after implantation (right).*

primary failure. In some cases both pathologies could be encountered in the same valve. This proportion varies considerably and could be seen reversed in some series of patients.

The causes for pericardial tears were described in detail<sup>18,19</sup> and can be summarised as an abrasive mechanism produced by the rubbing of the pericardium over the Dacron covered margin of the supporting stent. Such tears progress slowly until a part of one of the cusps becomes flail and the amount of regurgitation increases Fig. 6. This explains the fact that there is no sudden catastrophic failure with the pericardial valve, except when the initial, obvious clinical signs and symptoms of incipient malfunction have been missed or disregarded by the treating physician or the patient.

There may be, in a minority of cases, some slightly different mechanisms of pericardial damage at points of three-dimensional flexure or perforation caused by the excessively long ends of sutures used in aortic valve replacement.

The pericardial valves in the mitral position develop mechanical dysfunction, abrasion and possible rupture earlier than in the aortic position. In the mitral position the left ventricular contraction develops, abruptly, a much higher pressure than the systemic diastolic pressure applied on closure of valves in the aortic position. In addition, the unnecessary use of the largest possible valve size increases the risk of mechanical damage through abrasion.. This practice is the relic of using, by necessity of its nature, the largest possible porcine valve.

Concerning the tearing of the cusps due to abrasion, it was considered that this happened more often in the Low-Profile Shiley valve compared with the Standard valve because of the reduction of the height of the stent. This is not the case as it was demonstrated by Christie and colleagues that the profile of the valve is not, per se, the important factor of stress. The important one was found to be the angle, inclination, that the tissue forms with the commissure at the stent post, and this angle varies considerably from one type of pericardial valve to another. Reducing the inclination increases the stress, and vice versa<sup>77</sup>.

The coaptation stitch, as believed by some, does not seem to be responsible for initiating cusp tears. In fact, it is involved only later when the abrasion lesion advanced from its origin (at around 4 or 8 o'clock ) at the bottom of the cusp to the top of the post, when the tear is completed and that part of the valve becomes flail. Fig 5.

Within the limitation of the intrinsic durability of the chemically-treated bovine pericardium,

various modifications, physical and chemical, could be employed to eliminate this type of failure and considerably extend the functioning life of this valve.

Several techniques have already been used in order to reduce or abolish 'abrasion', as described in this article. One of them being the modifications made under the name of the projected Ionescu-Shiley Optimograft.<sup>21</sup>

## Calcification

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*Cromwell was about to ravage Christianity, when a grain of sand became stuck in his ureter*

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Valve calcification is a local representation of a general biologic phenomenon which occurs under specific conditions in various parts of the body, especially in younger individuals. Valve calcification is known to have taken place in all types of tissue valves. Because some important details are not given in the reported series (age of patients, timing of occurrence, position of the valve, etc.) it is difficult to form a clear-cut conclusion in all situations.

One report on a large series of patients followed for 6 years, presented at a symposium in 1986<sup>62</sup>, gave clear and complete information regarding the relationship between valve calcification and the age of the patients at the time of valve implantation. The authors showed that in the groups of patients aged between 10 and 59 years, the incidence of valve calcification ranged from 31.8% (in the age group of 10 to 20 years) to 1.8% (in the group aged 50 to 59 years) to reach zero calcification in patients older than 70 years. Similar conclusion about the relationship between age and valve related complications were published about porcine valves.<sup>78,79</sup>

The clear demonstration of this inverse relationship between the age of the patient and the rate of valve calcification 'sounded an alarm bell' and started to change the way in which tissue valves (porcine aortic and bovine pericardium) should be used in the future, and indicated the direction in which potential future research should be concentrated in order to make tissue valves universally acceptable by young and old patients. At this moment in time, tissue valves are almost exclusively used in patients older than 65 years because in old age the process of calcification is considerably slowed down and also because the life of the valves may outlast the life of those patients who reach a 'respectable' age.

Most scientists who studied the pathophysiologic mechanism of bioprosthetic heart valve calcification attribute the initial and predominant mineralisation of devitalised connective tissue cells of the bioprosthetic tissue matrix to the unique calcium-binding properties of cells and their components<sup>80</sup>. Intact living cells have intracellular free calcium concentration of approximately 0.1mM, whereas extracellular free calcium is 1.000mM (10,000 fold gradient across the plasma membrane). Although calcium entry into cells is passive, cellular calcium is held low by energy-requiring metabolic processes, such as the Ca<sup>++</sup> ATPase pump and intracellular binding. In contrast, intracellular phosphorous levels are relatively high, especially in the membrane-bound organelles, such as mitochondria, the nucleus, and within the plasma and organelle membranes themselves, which contain phospholipids as well as enzymatic system metabolizing high energy phosphates. These are the sites of initial bioprosthetic heart valve mineralisation. In necrotic cells as well as in cells devitalised by aldehyde cross-linking, passive calcium entry occurs unimpeded, but the mechanisms for its removal are no longer active. It is presumed that the calcium influx leads to

hydroxyapatite formation with the compartmentalised intracellular phosphorous, and that these early nuclei progressively accumulate additional mineral, becoming in time, macroscopic crystal formations<sup>81</sup>. Of related interest is the mitochondrial calcification, which has been extensively studied in myocardial infarction.<sup>82</sup>

It is well established now that the calcification is modulated through a complex inter-play of host and implant factors<sup>81</sup>. The possible interventions for mitigating or eliminating valve calcification are measures directed to either one of these two elements. Any intervention on the host appears to be extremely remote at present. Serious scientific research will have to continue, beyond present knowledge, in the hope that a successful solution will be found to prevent - at tissue valve level - the occurrence and progression of calcification.

Because, at present, none of these two interventions mentioned above are effective, the surgical community had opted for a third avenue. Knowing that the calcification of glutaraldehyde-treated pericardium represents two-thirds of the rate of structural valve failure and that this pathological process develops progressively and much slower in older persons (above 65-70 years of age) it seemed logical and safer to restrict the use of pericardial valves to older persons, those above the age of 70 years.

It is also evident that aortic degenerative valve disease is far more often encountered in today's heart valve pathology than mitral valve disease. Therefore, the enormous majority of pericardial heart valves are implanted nowadays in the aortic position of males older than 70 years of age. The



past experience with the first generation of pericardial valves showed that, in general, long term results are better in patients with aortic than those with mitral valve implantation. There was no thrombotic obstruction reported in these patients and the embolic rates were extremely low. All these additional benefits, plus the excellent haemodynamic function, even in small size valves, tilted the balance towards the use of the second generation of pericardial valves

almost exclusively in the aortic position, of older patients.

In simple terms, with the exception of some technical improvements in the reduction of tissue tears due to abrasion which accounted only for about one quarter of pericardial valve dysfunction, the main difference between the first and the second generation of pericardial valves was made by shifting the 'target' from the general use - in all patients of all ages - to the restricted utilisation as mentioned above.

Some experimental work by Johnson and associates<sup>83</sup> was carried out on potential, preventative strategies like binding calcification inhibitors to glutaraldehyde-fixed tissue, removal or modification of calcifiable components of the valve, modification of glutaraldehyde fixation process and the use of tissue cross-linking agents other than glutaraldehyde: one example of this would be the use of calcium diphosphonate pre-treatment of the glutaraldehyde-fixed valve tissue.

Webb and colleagues<sup>84</sup> demonstrated inhibition of bioprosthetic heart valve calcification by the use of aminodiphosphonate covalently bound to residual aldehyde groups in an experimental model. Anti-calcification treatments, such as surfactants, applied to the leaflet tissue before implantation were considered to be effective in mitigating intrinsic calcification from extrinsic sites of calcium nucleation such as insudating plasma proteins and lipids.

Several attempts have been made in order to abolish or at least to delay the occurrence of calcification. Two chemical processes were put forward: the T6 (Sodium dodecyl sulphate) by Hancock Laboratory and the PV2 (Tweed 80) by Edwards Laboratory. The two chemical interventions had been tested in animals and in humans with unconvincing results. Subcutaneous implants, in rats, of

cusps of porcine valves and strips of pericardium showed some positive results for the porcine cusps only. However, care should be exercised in extrapolating such data obtained from subcutaneous implants in rats to intracardiac location and function of valves in humans.<sup>85</sup>

Jones<sup>86</sup> and associates using the well known sheep model, which is a rapidly, universally and highly calcifying model, implanted porcine and pericardial valves either 'standard' or pre-treated with the Hancock T6 or the Edwards PV2 processes. The results showed that these processes mitigated the calcification of porcine valves but did not have any effect on the pericardial valves. Gallo<sup>87</sup> conducted similar experiments using the same model as Jones and Ferrans and implanted Hancock porcine valves, with and without the T6 treatment, in the mitral and tricuspid positions of sheep. He found no significant difference in the amount of cusp calcification between the standard and the T6 treated valves, whether in the mitral or in the tricuspid position.

To our knowledge, up to the present time, there are no scientific publications on clinical series of patients with tissue valves, porcine aortic and bovine pericardium, treated with 'anti calcification' processes showing any reduction of valve calcification. Dimitri and colleagues<sup>88</sup> were unable to show any demonstrable advantage in their series of patients for the T6 process, a treatment purported to mitigate calcification.

The fact that tissue valves are used almost exclusively in patients older than 70 years, is evidence enough that these two chemical processes are ineffective.

It would be more rigorous scientifically and ethically if valve manufacturers, and also some cardiac surgeons, will refrain from presenting, among the qualities of a tissue valve the fact that, a particular valve is treated with an anti-calcification process implying its usefulness, unless verifiable, factual, published evidence is presented to support such a claim.

It will also be necessary to remember one of the rules of research: 'No miracles allowed!'. This is indeed a fundamental law of science.

Despite the lack of clinical evidence and despite the fact that we know very little about the exact causes of this extremely complex process of calcification, we try nevertheless to treat it !

When Gertrude Stein, the artist, was dying she kept repeating "What is the answer? What is the answer?". Just before she died she suddenly sat up and said : "But we don't even know the question yet!".

So we can postulate that unless we find out why the human valve calcifies, we are not going to find out why prosthetic tissue valves calcify.

Macro and microscopic pathology studies of failed porcine bioprostheses by Schoen and Cohn<sup>89</sup> showed in detail the process of tissue degeneration in valves with tears, calcification, or both. They consider that patients with porcine aortic bioprosthetic valves follow a clinical, satisfactory course for around 5 years after operation. Late deterioration of these valves frequently necessitates re-operation. They estimate the rate of failure at approximante 15 to 25%, 7 to 10 years after valve implantation. Gallo and his associates<sup>79</sup> describe in detail the rate of occurrence and timing of primary tissue failure with the Hancock porcine valve, and show a similar percentage of failures. The actuarial freedom from valve failure in the mitral position at 10 years is 69%, and in the aortic position only 53%.

The rate of tissue valve failure accelerated from the 3rd post-operative year in the mitral position, and from the 5th year in the aortic position with a precipitous fall during the 8th and 9th years of follow-up. They believed that the patient can be told that he or she had a 30% chance of requiring re-operation because of the porcine valve degeneration within the next 10 years. This general calculation does not take into account the other causes of valve 'problems' which may lead to re-operation or

some other morbidity during that period of time.

Goffin<sup>90</sup> showed in a comparative histological study of explanted porcine and pericardial valves that the microscopic pathologic changes were similar in these two types of tissue. Grabenwoger<sup>91</sup> found similar pathologic changes in the failed Sorin Pericarbon pericardial valve.

These long-term studies showed that both the porcine and the bovine material used for valve construction and their long-term behaviour is similar. In a simplified way, the main difference between these two types of valves is the haemodynamic superiority of the pericardial valve and its smaller risk for embolisation. But the overwhelming advantage of the pericardial valve remains the fact that, being a man-made device, it lends itself to a variety of changes in order to improve its performance.

In most published reports about tissue heart valve replacement there are differences in the presentation of data and of the results in all aspects of a particular topic between the various publications. In almost all chapters of valve function, with the exception of haemodynamic and hydraulic measurements – which are scientifically obtained and mathematically expressed – there are differences from author to author. Why in the hands of one surgeon, the same type of tissue valve from the same manufacturer fails in one patient at 24 months, and in another one it lasts over 320 months? Microscopic studies performed on porcine and pericardial valves, explanted for various reasons between 12 months and 6 years, all showed gross histological changes in the structure of tissue.<sup>90,91</sup> In view of such changes in those valves, how did some of the porcine and pericardial valves continue to function well beyond 10 years and several valves well beyond 20 years? Why did the rate of occurrence of bacterial endocarditis differ from one hospital to another, and the embolic rate vary from surgeon to surgeon?

Certainly the host factor has not been seriously considered.

Some common sense and practical observations in this field give us some tentative answers. There are, generally speaking, several potential factors which may affect variously the durability of tissue valves, and which may explain the discrepancy among published results. Carlos Duran<sup>92</sup> summarised some of them in the following way:

- Variations at manufacturing level: Selection of tissue according to age of animal, thickness of the material in relation to the size of the valve to be constructed. The handling of the tissue from harvesting to the finished product. The design, chemical treatment and technique of construction of the device.
- About the patient: Complete information about the age and biological condition of the patient, history of other pathologies, heart rhythm, previous embolic episodes, anticoagulant treatment, etc.
- Concerning the surgeon: Correct rinsing of the bioprosthesis prior to implantation, maintaining the moistness of the valve throughout the time of implantation, careful handling of the device, extra care for the sterility and against possible contamination, correct positioning of the valve within the heart, especially in the mitral position, to avoid ‘asymmetrical opening of the cusps’<sup>93</sup> The avoidance of trying to implant the largest possible valve in the respective heart annulus. All pericardial valves are large enough for the corresponding orifice in which they are supposed to be fitted comfortably.

Great damage can be inflicted on a bioprosthesis at the time of implantation<sup>94</sup>. One of the not so rare causes is allowing the cusps of the valve to become dry – at times looking like parchment – during the time of placement of sutures. Some incredible errors occurred exceptionally: the plastic identification tag remained attached to the valve and became stuck to the left ventricle wall; the

sutures meant to secure the introducer were not removed and all three cusps of a valve were limited in their movement; entangling sutures around the stent struts, sometimes around two struts: (one of the incidents was published under the title of 'Fatal bioprosthetic regurgitation immediately after mitral and tricuspid valve replacement with Ionescu-Shiley bioprosthesis'<sup>95</sup>). This type of valve failure should have been called simply 'surgical failure'.

The 'family feud' between the porcine Montagues and the pericardial Capulets has been almost solved, not by words, but by time. This impartial arbiter has looked at facts and results.

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*What is now proven was once only imagined*

William Blake (1757-1827)

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A careful appraisal of the results and the evolution of the two types of tissue valves created and used during the past four decades brings into focus the similarities but mainly the discrepancies which set them apart as structures and as functioning valves. The porcine valve was subjected to several modifications which reached the limits imposed by the fixed geometry of the pig's aortic valve. The pericardial valve, the embodiment of the concept of 'man-made' devices, lends itself to an infinite permutation of changes of shape and physico-chemical interventions in order to improve its function, and indeed this is what happened. Almost 10 years after the creation, by Ionescu, of the pericardial valve, the concept behind it attracted several specialised laboratories to study this valve, to modify and improve it and bring it anew into the clinical field of usage, under different shapes and names, but always following the same general concept: glutaraldehyde-treated bovine pericardium mounted on a flexible frame as a three-cusp valve.

The prediction made by Ionescu when he created the concept of the man-made valve has proved to be not only true but extremely useful.

He might not have attained his dream of creating a perduring tissue valve to be used without anticoagulants, but he came very close to it; and we hope that the dream will continue to inspire his successors.

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*Examine your yesterday's ledger and you will find that you are still indebted to people and to life*

Khalil Gibran (1883-1931)

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## Chapter 2

# The Second Generation of Pericardial Valves

And an Interview with Marian Ionescu

*Paul Modi*

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*“Science commits suicide when it adopts a creed,  
when it becomes dogma”*

Thomas Henry Huxley (1825-1895)

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When I decided to write about the second generation of pericardial valves, I had to consider many things primarily related to: why did it happen at that time, why was bovine pericardium chosen and especially how could one explain the great leap from porcine valves to the pericardial ones? I would not find these answers any other place than at the source.

I visited Mr Marian Ionescu at his home and what happened there was more than I expected. We talked, despite the years which separated us, like old colleagues about anything and everything. The enormous leap from the pig valve to the pericardial valve cannot be simply and logically explained. As Newton once explained how he had discovered the law of universal gravitation, he said: "By thinking on it continually I keep the subject constantly before me and wait till the first dawns open slowly, by little and little, into a full and clear light." This pattern of consistent, almost relentless questioning, led to a depth of understanding and reconstruction of previous theories about the universe. But that, Mr Ionescu rightly considered, was for a man of genius. For us simple mortals any original thought must meet a prepared mind and even then one occasionally has to look beyond the horizon. You never know, he said, you may be surprised!

But an original idea is only a part of a concept which represents a complex intellectual entity. Concepts are imaginative glimpses, the authenticity of which must thereafter be tested against the truth of reality and their duration in time. But how to translate an idea into reality is something different. It is an instinctive process or simply the will of our curiosity to push it to the end, if that end exists.

Mr Ionescu was an inspirational character and one could tell he still possessed a passion for scientific discovery and cardiac surgery, as well as the dissemination of knowledge. He reminded me of a discussion between two giants of science: Niels Bohr and Wolfgang Pauli: 'You think I am crazy?' Bohr: 'I am afraid you are not crazy enough!'

Mr Ionescu spent a quarter of a century at the General Infirmary in Leeds, the most exciting and productive years of his surgical life, where he created, among many other interesting things, the pericardial valve. The first home-made pericardial valves were implanted in patients from April 1971 onwards and for the first five years nothing was published, awaiting - like Bedouins in the desert - to see whether a storm may appear. During these five years it became clear that the haemodynamic performance of these valves was excellent, thrombotic obstruction of the valves did not occur and long-term anticoagulant treatment was not necessary because the embolic rate was very low.

He confessed that he did not fully understand the essentials about embolism. What is exactly their nature, their origin and how to design an experimental model to further study them? He recounted this wisdom to me, without remembering its origin: 'Only when we know little do we know anything, doubt grows with knowledge'. In the end he said 'OK, let's consider that, for the time being, embolism is a solution in search of a problem'.

Five years later the fact that a new and different type of valve had functioned well and without signs of structural valve deterioration was considered encouraging and the results from that experience were published. Neither Ionescu, nor any of his associates have ever made any predictions or foolish promises about the long-term durability of pericardial valves. In fact he told me that at the beginning of this venture he did not have a clear idea about the potential durability of the pericardial valve, he only hoped that it would not deteriorate too soon but certainly did not believe that it would last forever.



The surgical community received this valve with enthusiasm because of these good results and on the belief that it must therefore have a good durability, it became considered the panacea for

heart valve replacement in all patients and at all ages. A further five years later, the haemodynamic performance and the reduced risk of embolism were maintained and the original results were reproduced and documented in many published series of patients. At about that time, structural valve deterioration began to progressively appear, more in the mitral than in the aortic position. This was a great disappointment for everybody and for some surgeons it was considered almost a betrayal of their own expectations based on nothing more than their own exaggerated desire or wishes.

During the ten years of worldwide use of the Shiley pericardial valves, five international symposia were organised in: Chamonix - France, Pebble Beach - California, Montreaux - Switzerland, and twice in London. These symposia were followed by the publication of their proceedings (five volumes). In addition, numerous scientific articles were published in specialised journals, all of them about the pericardial valve.

Towards the end of our discussions, Ionescu told me of yet another moment from the past, from the world of Giants. It was recognised by many that Otto Warburg's scientific writings were the clearest and the most precisely written articles. Only Szent Gyorgyi, who was of a similar standing in that world of Nobel Prize winners, dared to ask 'How do you do it?' The answer was prompt, simple and honest: 'I re-write them sixteen times!' I am sure that this was a veiled advice for my intention to write about the pericardial valves.

Most of the experienced, astute surgeons knew about Hermann's rule: 'Whatever you do, if you get it right the first time, you must have done something wrong', and they looked at the whole evolution of this valve as being the future of heart valve substitutes. The basis of Ionescu's pericardial valve concept carried with it from the beginning the possibility of design change to modify or improve it. Some people realised that the potential of this valve was therefore considerable and that changes could and should be made to improve its durability while maintaining the integrity of the basic structure.

The large amount of results documented during its clinical use over a period of fifteen years triggered two important fields of research. The first was in the field of structural valve deterioration (calcification and cusp tears) and by better understanding the process of tissue calcification it was hoped that this would lead to measures to prevent or retard the occurrence of calcification of chemically-treated (glutaraldehyde) pericardial tissue. The second line of research was directed at the physics, dynamics and mathematical calculations for a better, more scientific approach to the 'stent-valve complex' construction and tissue mounting.

A large number of scientists and dedicated researchers contributed to this effort and much important work was accomplished and published. Unfortunately, in spite of very interesting results, they have not succeeded in finding a solution for the prevention of calcification of pericardial valves. The complication of cusp tears due to abrasion of pericardium against the Dacron covering of the stent was remedied by various ingenious techniques of tissue mounting onto the stents, as will be described further in this text.

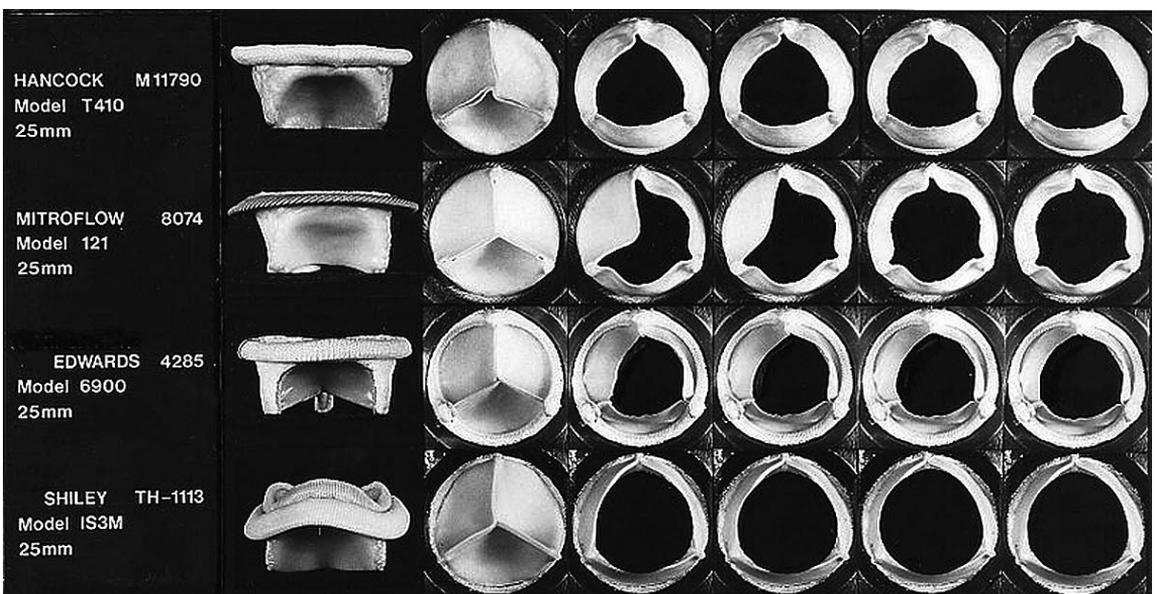
Another consequence of the usage of the Shiley pericardial valves was the realisation that tissue calcification was age-dependent with the calcification process progressing more slowly in patients older than 65 years. Consequently it was decided to shift the goal of pericardial valve usage from all patients of all ages to only patients aged more than 65 years. In this way, the problem of valve calcification was considerably reduced, not by a chemical treatment but by transferring it to a different biological terrain.

The improvement in the techniques of mounting the pericardium onto the stent helped to reduce the rate of pericardial cusp tears. Based on these new premises, derived from the experience

and knowledge gathered with the first pericardial valves, a second generation of such valves began to be manufactured and brought into clinical use. The originality of the concept, the successes and failures, the flaws and positive aspects of the original pericardial valve and the experience accumulated with its use over the first 10 to 15 years, together with the results obtained by scientific research, created the incentive and showed the way for changes, modifications and potential improvements in the manufacture of these second generation valves. There were too many to all mention here - tricuspid, bicuspid and even a monocusp pericardial valve were brought to the market by their protagonists shortly after some articles about the failings of the Shiley valve were published. It so happened that some of these inventions did not last more than several months until they had to be withdrawn from use.

Of the many pericardial valves developed since 1980, only three have stood the test of time. These three modified and improved pericardial valves were made by very gifted technicians at three laboratories: Mitral Medical Inc. (which later became part of the Sorin group), Edwards Laboratories (now Edwards Lifesciences)<sup>1</sup> and the Sorin Group<sup>2</sup>. All three laboratories have devised different techniques of valve construction with the aim of reducing or abolishing the risk of tissue abrasion. The specialists at Mitral Medical Inc. retained the technique of mounting the pericardium outside the stent as in the original Ionescu valve, but found later another and better way of reducing abrasion. The Edwards engineers used an ingenious way of mounting the pericardium inside the stent albeit with a minimal loss of useful opening to flow area. The Sorin technicians devised yet another way of mounting the pericardium in a double layer so as to have the stent margin padded with a pericardial sheet (similar to one of Ionescu's modifications, the Optimagraft)<sup>3</sup>.

The Mitroflow valve, as first manufactured by Mitral Medical in 1982, had to be redesigned because it showed a failure mode similar to the first generation of pericardial valves. Since 1991 a modified version of this valve was introduced and has been used in a large number of patients<sup>4</sup>.



*Fig 1: The opening characteristics of 4 pericardial valves - Hancock (no longer available), Mitroflow, Edwards and Shiley. All 4 valves were manufactured for clinical use and all were 25mm in diameter. The valves were photographed under identical conditions in the mitral side of a 'pulse duplicator' and the flow rates at peak diastole were: for each frame, from left to right: 0, 100, 200, 300, and 400mls/sec.*

The Edwards valve became available in 1980. The device made in the configuration for mitral replacement had to be withdrawn after implantation in a small number of patients because of excessive flexibility of the stent causing mitral incompetence. A new redesigned version of this valve was reintroduced in 1984<sup>5</sup>. The additional changes made in the configuration of these two valves demonstrate once again the advantage of the versatility of the ‘man-made concept’ of the pericardial valve.

The haemodynamic characteristics of these 3 types of valve<sup>6,7</sup> are similar to the excellent results found with the original Ionescu-Shiley valve as first described by Tandon’s group<sup>8</sup>. The minor differences in gradients and calculated orifice area are not clinically significant. The images portrayed in Figure 1 show the opening characteristics of 4 pericardial valves – Hancock (no longer available), Mitroflow, Edwards and Shiley. The cusps of these valves open synchronously up to a very large surface area with only minimal difference from one valve to another.

Regarding other complications (embolic, anticoagulant-related haemorrhage and endocarditis), there is only scant data in the publications analysed for this article. It is presumed, and not without good reason, that the main emphasis was placed by the authors on structural valve deterioration (SVD). It can also be considered logical that complications of these three types of pericardial valves would occur at about the same rate as those of the original Ionescu valve due to their similar structure and dynamic function

The scientific publications on these three 2nd generation pericardial valves are not only few in number but they lack some of the necessary standardized data for a complete, clear and fair evaluation and comparison of results of the different publications. In order to avoid generalities and averages, the data reporting SVD are presented in the form of tables.

Table 1. Mitroflow Pericardial Valve

Main Author/year	No of patients Valve location	Patient mean Age (range)	No of SVD, position	Actuarial freedom from SVD-years
Revuelta, 1990 <sup>9</sup>	130-All, 90-A, 27-M, 10-D	55.4 (26-74)	1 Aortic, 4 Mitral	At 7 years, all valves 86%
Loisance, 1993 <sup>10</sup>	199-All, 107-A, 63-M, 28-D, 1-T	58		At 5 years 94.6%. At 10 years 63.7%
Sjogren, 2006 <sup>11</sup>	152 Aortic	79.5 (75-91)		At 5 years 99%; At 10 years 82%
Benthamien, 2008 <sup>12</sup>	161 Aortic	69.5 (60-94)	19 in group 60-69, 6 in group >70 years	At 15 years 60-70- 62%; >70 -73%
Yankah, 2008 <sup>13</sup>	1513 Aortic	72.4	122. Stenosis 36.7%, regurgitation 20;4%, both 42.9%	At 20 years <65 -71.8%, >70 -84.8%
Jamieson, 2009 <sup>14</sup>	381 Aortic from 3 centres	76;4 (53-91)		At 10 years: <60 -85.2%; >60-85%, 61- 70 95.7%, >70-83.2%

A = Aortic, M = Mitral, D = Mitral and Aortic, T = Tricuspid, SVD = Structural Valve Deterioration

The lack of standardised data presented in these publications makes interpretation difficult. The discrepancy of the actuarially presented results between the various publications is evident.

Table 2. Edwards Pericardial Valve

Main Author/ year	No of patients. Valve position	Patient mean age (range)	No of SVD, position	Actuarial freedom from SVD - years
Pelletier, 1990 <sup>5</sup>	284- All, 222-A, 77-M, 2-T	58 <sup>19-79</sup>	3 valves, 1 M regurgitation at 26months, 2 A - thrombus at 20 months, tear at 68 months	Reoperation for all causes SBE, SVD, and perivalvular leak. Overall 92% at 6 years
Jamieson, 1999 Multicentre report <sup>15</sup>	429 all Mitral, 318-M, 101-D	60.7	Calcification 70 .4%, leaflet tear 18.5%, both 11.1%	At 10 years: age<40 - 80%, 41-50 -91%, 51- 60 - 84%, 61-70 - 95%
Marchand, 2001 <sup>16</sup>	435 all Mitral, 333-M, 102-D	60.7 <sup>8-82</sup>	56 episodes: calcification 73%, tears 20% both 7%. Duration to explant 9.5 years (5-13.6)	At 14 years: all patients 66.3%, < 65- 62.8%, >65 -85.9%
Biglioli, 2004 <sup>17</sup>	327 all Aortic, 298 study group	67.2 (19-83), 215 patients aged>65	Considerable increase on the risk of prostheses replacement after 10 years post-op	At 14 years: all patients 52.9%, <65 -35.8%, >65 -83.7%
McClure, 2010 <sup>18</sup>	1000 all Aortic	74.1	26 valves	At 15 years: age<65 -34.7%, 65-75 - 89.4%, > 75- 99.5%
Welke, 2011 <sup>19</sup>	2168 all Aortic	21 to over 75 years	Not mentioned	At 10 years: Age 21-49 58% 50-64 -68% 65-74 - 93% > 75 -99%

A =Aortic, M =Mitral, T = Tricuspid, SVD = Structural Valve Deterioration, SBE = Subacute Bacterial Endocarditis

The inverse relationship between the age of the patients and the rate of SVD is obvious in most reports. There are very significant differences among the various publications concerning the figures of actuarial freedom from SVD. Data from Carpentier’s group can be found in reference 20.



Table 3. Sorin Pericardial Valve

Main Author/ year	No of patients. Valve location	Patient mean age (range)	No of SVD, position	Actuarial freedom from SVD - years
Folliguet, 2009 <sup>21</sup>	277 all. 224 -A, 39 -M, 10 -D, 3-P	178 > 75 years (64.3%)	3 aortic, 2 at 7 years, 1 at 2 years	At 10 years: all patients -96.6%, Aortic -96.1%, Mitral - 100% (i)
Grabenwoger, 1994 <sup>22</sup>	144 all.. 114 -A, 25 -M, 5 - D	69	9 valves, 3 mitral, 6 aortic, 7 stenotic, 2 regurgitant, 9 calcified. Valve failure at +/- 55 months post implant	See below (ii)
Caimmi, 1998 <sup>23</sup>	78 all mitral	56.9	26 calcified-stenosis	At 12 years: 56.8% all . < 60 -36.8%, >60 -86.3%
Seguin, 1998 Multicentre report <sup>24</sup>	321 aortic	75.8	6 valves - calcification	At 10 years -83.9%

A = Aortic, M = Mitral, D = Mitral and Aortic, T = Tricuspid, P = Pulmonary, SVD = Structural Valve Deterioration.

(i) This figure should be interpreted with caution because the study was of only 39 patients with mitral replacement and only 2 patients were at risk at 10 years. The patients' ages were not shown with details.

(ii) This study describes only the pathology of failed valves in 9 patients (out of a series of 144), 51 to 79 years old (mean 69) followed-up for 6 to 8 years. The description of clinical use and results of the 144 patients who received Sorin Pericarbon Pericardial Valves would have been of great interest, but a search through the relevant medical literature has not found any such publication from the surgical team.

The symptoms of valvular stenosis due to calcification are insidious and often well tolerated by the patient. The reported actuarial figures of freedom from SVD may therefore, in fact, be different if the valves had been assessed by echocardiography. This pertains to the figures in all three tables.

There are very few published reports containing sufficient data in order to be useful. One can only note, without much comment, the gross difference between the number and percentages of SVD shown in these three tables. However, in spite of some failings in reporting and the variability of the results in the different series, the considerable increase in valve durability of the second generation pericardial valves is quite evident. This is the best clinical evidence that over a long period of time, calcification, which was the main cause of pericardial valve failure (about 80% of SVD), could be controlled albeit with Nature's help.

### Can a meaningful comparison be made between the Ionescu-Shiley and 2nd generation valves?

A scientific comparison among these 3 second generation valves, and between them and the Ionescu-Shiley valve is practically impossible. The number of patients in the published series varies considerably. In addition there had been an almost equal distribution of mitral and aortic

replacements with the Shiley valves, while for the second generation valves the ratio was about 1:8 in favour of the aortic valve. The much smaller number of mitral valve replacements in the second generation series of patients is due, in part, to the reduction of rheumatic mitral valvular disease in the western world and at the same time because of the proportional increase in the number of patients with degenerative aortic valve disease in a progressively aging population. Another reason appears to be the knowledge that pericardial valves in the mitral position are more susceptible to SVD than in the aortic position, for reasons described in the first chapter.

Another confounding factor is that during the 1970s and 80s, Shiley pericardial valves had been used in patients of all ages, and particularly in patients under the age of 65 years. During the 1990s and into the following decade, the mean age of patients receiving the second generation of pericardial valves varied between 67.2 and 72 years, a very significant difference in age. Thus the inverse relationship between patient age and valve calcification confounds a meaningful comparison. To a certain extent this relationship was known beforehand from the porcine valve experience but it had not received sufficient emphasis until the use of pericardial valves.

Additionally, the time-frame of their usage also varied (1971 to 1986 for the Shiley valves and 1981 onwards for the second generation valves). Surgical techniques and experience in general have evolved over the past 40 years and the lessons from the past might have borne fruit.

The experience with the Shiley valves showed that 75–80% of valve failure was due to calcification and only 20–25% failed because of tissue abrasion and cusp tears. These figures are similar in percentages between the Shiley and the second generation valves (when the latter were used in younger patients and in all cardiac positions) as shown in Table 4. The technical improvements made in the second generation of valves has virtually eliminated cusp tear due to abrasion,

*Table 4. Actuarial values of freedom from structural valve deterioration (SVD) at 10 years or more of follow-up in patients younger than 65 years*

Valve Manufacturer	Author/ Year	Implant position	Duration of study - Freedom from SVD %
Edwards	McClure 2010 <sup>18</sup>	A	At 15 years: 34.7. CI: 6-67
Edwards	Biglioli 2004 <sup>17</sup>	A	At 14 years 35.8 +/- 10.7
Edwards	Poirier 1998 <sup>25</sup>	A	At 10 years . 84.7
Edwards	Welke 2011 <sup>19</sup>	A	At 10 years 63
Edwards	Weber 2012 <sup>26</sup>	A	At 10 years 59.5
Edwards	Banbury 2001 <sup>27</sup>	A	At 10 years 48
Edwards	Jamieson 1999 <sup>15</sup>	M	At 10 years 80
Mitroflow	Yankah 2008 <sup>13</sup>	A	At 20 years 71.8
Mitroflow	Jamieson 2009 <sup>14</sup>	A	At 10 years 85
Sorin	Caimmi 1998 <sup>23</sup>	M	At 12 years 36.8

*A = Aortic, M = Mitral, CI = Confidence Intervals*

Despite claims that all 3 types of second generation valves were treated with ‘so-called’ anti-calcification processes, implying a clinical reduction of calcification, none of the published results have shown any benefits in patients whatsoever from such chemical treatments. The likely explanation for

the reduced rate of calcification and therefore of structural valve deterioration in patients receiving these second generation valves was the advanced age of the patients who received them. The age of the patients was shifted from a mean of around 50 years with Shiley valves, to a mean of more than 70 years with the second generation valves.

It is regrettable that pericardial valves, which are known to carry a very low risk of embolisation, could not be freely used in the mitral position where the need and benefit would have been greater. The main obstacle remains the risk of calcification. However, in general, the second generation pericardial valves represent a progress in the armoury of devices for the treatment of heart valve disease in older patients. If the process of valve calcification could be controlled through biochemical interventions, these pericardial valves would have the potential to come close to becoming the panacea for all patients in need of heart valve replacement. For the time being, however, we have to accept that the understanding of this phenomenon of 'calcification' and its prevention lies somewhere beyond the horizon.

It becomes obvious from this description that the two important creative stages in tissue heart valves (from 1964 to 1971) took place in a short space of seven years and that since 1971 when the concept of 'man-made pericardial valves' was created, the other great advance has been the transcatheter valve which follows the same concept: glutaraldehyde-treated pericardium supported by specially shaped frames and implanted transarterially or through the left ventricular apex, as will be described in a later chapter.

## Conclusions

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*It was by trying and by persisting  
That the Greeks took Troy*

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The bovine pericardial valve was created in 1971 in Leeds, UK, and over the ensuing four decades, with various modifications and improvements made by different laboratories, it became the tissue valve of choice for the great majority of surgical groups around the world.

The creation, within the pericardial valve concept, of the second generation of pericardial valves was a substantial improvement on the Ionescu valve by a considerable reduction in SVD, the main flaw of that original valve. This was achieved by two interventions: the changes made in the technique of tissue mounting onto the stent, thereby virtually eliminating abrasion and cusp tears (which represents approximately 20% of SVD); and by avoiding the risk of tissue calcification (approximately 80% of SVD) by implanting the second generation valves predominantly in patients over the age of 65 years in whom the natural calcification process is much slower.

The pericardial valve is not simply another valve, it is the embodiment of a concept of tissue valve construction. At present bovine pericardium is being used, tomorrow perchance an even better material may be found. In this respect, Ionescu made, in one of his early papers, a significant and rather prophetic statement:

*'The physico-chemical and biological properties of the natural porcine aortic valve have been profoundly altered by various interventions in order to adapt it for therapeutic means. In this way, the porcine valve has lost all its primordial characteristics except its shape which remains unchanged and unchangeable. The pericardial valve, on the other hand, has been conceived as an entirely 'man-made' valve and therefore its shape and general characteristics can be altered through a multitude of interventions in order to optimize its function'<sup>28</sup>.*

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## Chapter 3

# The Transcatheter Aortic Valve Implantation

Tavi - With particular emphases on the use of the Edwards SAPIEN pericardial valve

*Vinayak (Vinnie) Nilkanth Bapat  
Mohsin Uzzaman*

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*“Adhuc sub iudice lis est.”*

Quintus Horatius Flaccus (68 - 8BC)

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## Historical Perspective

The creation of the ‘man-made’ concept and the invention of the first glutaraldehyde-treated bovine pericardium, mounted onto a flexible stent, began in Leeds in April 1971.

This novel concept permits changes and improvements, as necessary, while maintaining its essential characteristics. In this way changes were made to build the second generation of pericardial valves and, more recently, to develop the TAVI principle - which is in progressive evolution.

The drive to develop a device for transcatheter implantation in the aortic position for valve replacement (TAVI), was specifically addressed to overcome the risk of early restenosis following balloon aortic valvuloplasty.<sup>1</sup> In 1993, Alain Cribier inserted 12 Palmaz stents in post-mortem obtained specimens of aortic stenotic valves and demonstrated that the idea of safely anchoring the stents in the aortic valve position was feasible and safe.<sup>1</sup> The first prototypes of balloon-expandable valves were developed by a start-up company, “Percutaneous Valve Technologies” (PVT New Jersey) and tested in an animal model in 2000<sup>1</sup>. The device consisted of a trileaflet bovine pericardial valve mounted in a single size (23 mm) stainless steel balloon-expandable stent. (Figure 1) The “first-in-man” TAVI was then performed by Cribier on April 16th, 2002 using this device<sup>2</sup>. The insertion of the device was performed on a 57-year-old man who presented with cardiogenic shock with major left ventricular dysfunction (ejection fraction 12%) and multiple comorbidities precluding a safe open aortic valve replacement (AVR). The presence of aorto-femoral bypass occlusion on one side and severe contralateral atherosclerosis prevented the use of the transfemoral retrograde access. The patient also had an intraventricular floating thrombus. TAVI was performed using the antegrade transseptal approach. The procedure was completed without complication. Haemodynamic and echocardiographic results showed significant improvement and the valve function was excellent, as demonstrated by transoesophageal echocardiography<sup>2</sup>. This patient provided the evidence needed to pursue further development of this novel procedure.

Since then, this technique has undergone rapid developments and refinements during the last decade. Since the Edwards SAPIEN transcatheter heart valve and the Medtronic CoreValve System have become commercially available, more than 80,000 patients have undergone TAVI around the world<sup>3</sup>.



Figure 1: SAPIEN valve models.

a) Original PVT valve b) SAPIEN c) SAPIEN XT d) SAPIEN 3

## Available Devices

Two types of devices are commercially available at the present time. They are either balloon expandable or self-expanding. A variety of devices using Nitinol are available. This is a self-expanding material, which allows the device to be crimped in a small diameter tube. The device expands to a predetermined shape at body temperature. The first self-expanding device available was the CoreValve (Medtronic Inc, Minneapolis, MN). It consisted of 3 porcine pericardial leaflets mounted into a long self-expanding multi-level Nitinol frame with 3 different areas of radial force. Due to its specific design, the CoreValve was built to be implanted intra-annularly but function supra-annularly. The CoreValve is currently available in 4 diameters 23, 26, 29, and 31 mm. Four other devices utilizing pericardium as leaflet tissue and Nitinol as stent frame are available. These are Engager (Medtronic Inc, Minneapolis, MN) with bovine pericardial leaflets, Portico (St. Jude Medical, Minneapolis, MN) with porcine pericardial skirt and bovine pericardial leaflets, JenaValve (JenaValve, Irvine, CA) with bovine pericardial leaflets and Sadra Lotus (Boston Scientific, Boston). (Figure 2) Each is available in 2 to 4 sizes.

The only balloon expandable TAVI device available is the Edwards SAPIEN® valve (Edwards Lifesciences). The first model was the SAPIEN® valve with three bovine pericardial leaflets mounted on a stainless steel frame.

## Edwards SPAPIEN Devices

### A) SAPIEN:

The first model was the SAPIEN® valve with three bovine pericardial leaflets mounted on a stainless steel frame. The inflow of the frame was covered with fabric to provide an annular seal. Three bovine pericardial leaflets similar to those used in the standard stented valves were sutured to the stent and the fabric (Figure 1b). Leaflets were treated with ThermaFix anticalcification process. This method combines glutaraldehyde fixation for structural stabilization, the XenoLogiX (Edwards Lifesciences) treatment for extraction of phospholipids, and a new, mild heat treatment that removes unstable glutaraldehyde moieties.

It is necessary to mention here that the purported 'anti-calcification treatment' described above is only the manufacture's claim for a commercial product and does not represent any clinical reality until, and unless, scientifically proven through verifiable published results of long-term studies.

The follow-up of patients with TAVI is less than 10 years, while the calcification phenomenon

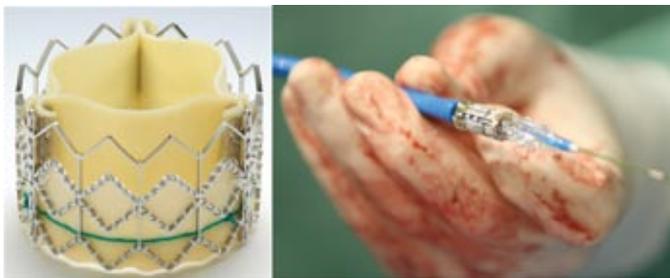


Figure 2: Self expanding TAVI devices with pericardial leaflets

a) Corevalve b) Engager c) Portico d) Sadra

occurs, especially in older patients, well beyond ten or fifteen years post-implantation;

In many clinical series published on the results of conventional stented pericardial valves, the efficacy of anti-calcification processes, in patients followed for more than 20 years has not been proven. (see Chapters 1 and 2 of this book.)



*Figure 3: SAPIEN device before and after crimping*

The Edwards SAPIEN valve was available in two sizes, 23mm and 26 mm and could be delivered through three routes, transfemoral (TF), transapical (TA) and subsequently trans-aortic (TAo). The delivery systems used were Retroflex (generation 1, 2, and 3) for TF and Ascendra 1 for TA and TAo. [4,5] The devices were crimped to be delivered through either 26 or 32 French size delivery systems. (Figure 3) Important dimensions of the devices are given in Table 1.

In a standard implantation procedure, each valve is crimped with its individual size-specific crimper to be implanted through a specifically sized sheath. Due to the crimping process, Edward SAPIEN valves are only available with pericardial leaflets as opposed to porcine valve leaflets, as it has been shown that pericardial leaflets tolerate crimping.

## **B) SAPIEN XT:**

The second generation SAPIEN the XT® valve is characterized by a low profile and a tubular cobalt chromium frame. (Figure 1c) With changes in design and materials the THV profiles could be downsized, which reduces the risk of vascular complications. Available sizes are 20, 23, 26 and 29 mm. The pericardial leaflets are constructed using the Leaflet Matching technology, and treated by the ThermoFix ‘anticalcification process’. The SAPIEN XT 23 mm and 26 mm are accommodated by 22 Fr or 24 Fr sheaths, respectively. The stress on the access vessel could be reduced with the introduction of expandable sheaths. Currently the SAPIEN XT 23 mm, 26 mm and 29 mm can be delivered by 16 Fr, 18 Fr and 20 Fr expandable sheaths, respectively. The dimension of the device is provided in Table 1.

## **C) SAPIEN S3:**

The most recent model of the SAPIEN device is the recently CE marked SAPIEN 3 (S3) valve. (Figure 1d) It was designed to address two issues with TAVI, paravalvular leak and crimp profile. The leaflet design and ‘anticalcification treatment’ is similar to that of SAPIEN XT. The S3 model incorporates a unique stent and leaflet design that allows for crimping to a further reduced profile of 14 and 16 Fr size<sup>6</sup>. As with its predecessors, the inflow of the S3 is covered by an internal polyethylene terephthalate (PET) skirt<sup>6</sup>. However, S3 incorporates an additional outer PET sealing cuff intended to reduce paravalvular regurgitation. (Figure 1d). Three sizes 23, 26 and 29 are now commercially available, while 20mm valve is undergoing CE mark trial<sup>6</sup>. The S3 device is however taller when compared to the previous iterations and the stent frame although made of cobalt-chromium has a different structure with unequal cells. (Figure 1d and Table 1).

*Table 1. Edward Sapien and Sapien XT models with their sizes and dimensions*

Valve-type	Bioprosthesis diameter (mm)	Annulus size (mm)	Frame-Height (mm)
Sapien	23	18-22	14.3
Sapien	26	21-25	16.1
XT Sapien	23	18-22	14
XT Sapien	26	22-25	17
XT	29	25-27.7	19

## Technical considerations for TAVI

Performance of TAVI using Edward SAPIEN pericardial valves should be restricted to high-volume medico-surgical centers with expertise in valve disease. All the physicians involved in TAVI programs should have previously received specific training. Ideally, TAVI should be performed in “hybrid” rooms, combining the specific characteristics of both the catheterization laboratory and the operating room, with the immediate availability of circulatory assistance if needed.

The decision to perform TAVI under general anesthesia depends mainly on the need for transoesophageal echocardiogram (TEE) guidance, the requirement for surgical arterial or thoracic access, or local preferences. However, with the increasing experience of the operators and the reduction of the introducer diameters, the proportion of TF procedures performed under sedation, and local anesthesia tends to increase. A strict haemodynamic monitoring is crucial, with the objective of maintaining a systolic aortic pressure between 110 and 130 mmHg throughout the procedure. This justifies the presence of an anesthetist in all the cases.

Prophylactic antibiotics are given at the beginning of the procedure and intravenous anticoagulation with unfractionated heparin is administered, with a target Activated Clotting Time between 250 and 300 seconds. Heparin can be reversed at the end of the procedure. By default, the access is most often TF.<sup>7</sup> If this is not possible, the alternative approach depends on the type of the prosthesis used and local preferences. The TA route is possible with the SAPIEN valve.<sup>8</sup> More recently, there has been an increasing interest for the TAO access as it avoids the drawbacks of the ventricular puncture required for TA.<sup>10</sup>

The different steps of implanting an Edwards SAPIEN Valves are as follows.<sup>7-9</sup> After obtaining arterial or thoracic access, the main steps include retro- or antegrade crossing of the aortic valve, placement of a stiff wire through the valve, and predilatation of the valve with an undersized balloon. Then, the Edwards SAPIEN prosthesis is placed at the level of the aortic orifice and deployed. Precise positioning of the prosthesis warrants prior identification of the plane of the annulus, which is usually represented by the projection where the 3 cusps are seen on the same line. Optimal projection can be determined by conventional angiography or by using software allowing for the identification of a perpendicularity line. The SAPIEN valve is deployed by inflation of the balloon under rapid ventricular pacing (usually 180 to 220 bpm), with the objective to decrease aortic pressure below 50 mmHg in order to avoid cardiac motion, transaortic flow, and ejection of the prosthesis towards the ascending aorta. Immediate assessment of the result is crucial and involves an accurate analysis of the ECG (possible rhythm and conduction disturbances and myocardial ischemia), the TTE/TEE (possible pericardial effusion, left ventricular function, detection of a

possible central, or paravalvular regurgitation) and an angiogram (prosthesis positioning, coronary patency, and potential aortic regurgitation).

Post-procedural care is also crucial. Patients are transferred to an intensive or coronary care unit for at least 24 to 48 hours, and can be discharged between day 5 to day 10, if no complication occurs. In addition to standard clinical and biological parameters, post-procedural monitoring should focus on vascular or thoracic access sites, conduction disturbances (which may be delayed) and arrhythmias (in particular atrial fibrillation with its inherent risk of stroke) and on valve function, which should be carefully assessed by TTE before discharge. Unless oral anticoagulant therapy is needed, a combination of aspirin and clopidogrel is empirically recommended for 3 to 6 months. The duration of treatment may be shortened for patients at high risk of bleeding.

## Procedural Complications

There are several serious procedural complications that may occur during TAVI. Patients may transiently develop shock and low cardiac output states following rapid pacing, required to prevent movement during SAPIEN valve deployment. This may require temporary haemodynamic support. Rarely, coronary artery obstruction may occur (1%-2%) – especially with low coronary ostia heights < 10mm, small coronary sinuses, or with bulky displaced native leaflet calcification<sup>11-13</sup>. Annular rupture, aortic dissection, or valve embolization (< 1%) are rare, but may require pericardiocentesis or emergency median sternotomy with open surgical repair. Complete heart block requiring permanent pacemaker placement (especially with a preexisting right bundle branch block) occurred in 5-10% of patients. The need for permanent pacemaker is higher with the Corevalve (21%) compared with the SAPIEN XT valve (6%) due to extension of the self-expanding Nitinol cage within the left ventricular outflow track<sup>14</sup>.

Vascular complications occur in approximately 10% of patients, including iliac artery dissection, perforation or avulsion<sup>11,12</sup>. Most can be treated percutaneously with stents or stent grafts, but with proper procedural planning and vessel sizing, many vascular complications can be avoided. Major vascular complications are associated with an increase in late mortality.

Paravalvular regurgitation occurs in nearly 85% of TAVI patients as a result of incomplete apposition of the valve prosthesis within the aortic annulus due to inadequate inflation and expansion of the prosthesis or calcific deposits that prevent proper seating<sup>11,12</sup>. In the PARTNERS Trial, moderate or severe paravalvular aortic regurgitation was more frequent after TAVI compared with standard aortic valve replacement (SAVR) at 30 days and up to 2 years (6.9% vs. 0.9%)<sup>11,12</sup>. Any more than trivial paravalvular regurgitation is associated with an increased late mortality at 2 years (hazard ratio 2.11, 95% CI 1.43-3.10), but it is uncertain if the aortic insufficiency itself is a cause of late mortality or just a marker of increased risk.

Stroke occurs in 4%-8% of patients after TAVI<sup>15,16</sup>. There is a cluster of stroke events very early after the procedure; 70% of the events occurred within 48 hours, and 96% occurred within the first 9 days<sup>11,12</sup>. Beyond 30 days, the incidence of any neurologic event (stroke/transient ischemic attack) was comparable between groups (4.4%, TAVI vs 4.5%, SAVR, P = 1.0)<sup>11,12</sup>. The main causes of stroke are due to aortic arch or ascending aorta atheroemboli<sup>15,16</sup>. Other potential causes include calcific embolism from the aortic valve, embolism from catheters, air embolism from left ventricular cannulation with the TA approach, prolonged hypotension, and dissection of arch vessels<sup>15,16</sup>. Repeated or overly aggressive valvuloplasty might be associated with an increased risk for embolization of calcific material from the aortic valve and should be avoided<sup>15,16</sup>. The rate of

stroke has fallen over time with improved procedural technique, improved delivery systems, and more aggressive anticoagulation. MRI-detected “silent” embolic events occur in nearly 85% of TAVI procedures<sup>17</sup>. Embolic protection filter devices delivered from the radial artery to shield the aortic arch vessels are being tested in clinical trials.

The management of complications can be summarized by the following five points: 1) prevention, assured by a meticulous screening; 2) anticipation, achieved through a thorough multidisciplinary evaluation; 3) immediate identification; 4) the training of the teams to deal with ‘bail-out’ equipment and procedures; 5) when necessary, the immediate availability of cardiopulmonary support and conversion to surgical intervention.

## Case Selection for TAVI

Patient selection for Edwards SAPIENT<sup>THV</sup> is a crucial process, of which every single detail counts. It should involve a “heart team” which includes cardiologists, cardiac surgeons, imaging specialists, anesthetist with experience in valve disease, and other specialists such as geriatricians if necessary. To begin with, it is necessary to determine the indication for the procedure including an evaluation of the level of surgical risk. This assessment is based on clinical judgment, supported by quantitative predictive risk scores, mainly the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) and the Euro-SCORE<sup>11,12</sup>. Patients are seen by a multidisciplinary team including at least two cardiac surgeons and an interventional cardiologist. Although these scores provide precious guidance for patient selection, they tend to overestimate operative mortality in high-risk patients, and do not take into account many important comorbidities (porcelain aorta, liver cirrhosis, kyphoscoliosis, previous sternotomies etc.) as well as patient frailty, whose prognostic impact is significant in this elderly population<sup>11</sup>. Secondly, it is necessary to assess the technical feasibility of TAVI, which is conditioned by the patient’s anatomy. This evaluation is based on multimodal imaging combining transthoracic (TTE) and/or transesophageal echocardiography (TEE), multislice computed tomography (MSCT), and conventional angiography. The main targets are the arterial access sites (diameters, calcification, tortuosity) and the aorto-valvular complex, consisting of the aortic root, the aortic annulus, and the left ventricular outflow tract. The information obtained from this evaluation will allow the determination of the best approach for the Edwards SAPIENT Valve (TETA, TAO) and the most suitable type and diameter of valve, and to anticipate possible strategies or complications during the procedure. Finally, the patient’s coronary status should be assessed, although there is currently no specific recommendation concerning coronary revascularization in this setting. Indeed, such a decision should take into account symptoms, clinical condition, extent of myocardium at risk, and coronary lesion characteristics.

## Evidence

Since 2007, several multicenter registries using either or both of the commercially available transcatheter heart valves have been conducted. These registries have contributed to technological improvements as well as increased knowledge concerning patient selection and prevention and management of complications. The publication and dissemination of data from several centres helped to obtain an improvement of up to 97% in the success of this procedure. The excellent haemodynamic performance of the pericardial valves has been confirmed, as well as the favorable

impact on symptoms and the survival rate of patients. Among these studies, 2 large European registries are particularly interesting: SOURCE<sup>10</sup> and FRANCE 2<sup>18</sup>. The SOURCE registry used the SAPIEN valve and included 1038 patients from 32 centers<sup>10</sup>. Overall, patients treated with the TA approach represented a higher-risk population in comparison to those treated with the TF approach, however, the immediate success rate was 94% for all patients. Thirty-day mortality was higher among the TA group (10.3 %) in comparison with the TF group (6.3 %) <sup>10</sup>. Furthermore, the occurrence of vascular complications was not associated with an increase in 30-day mortality for the TF group. At 1-year, the survival rate was 76.1% in the whole cohort (72.1% in the TA group and 81.1 % in the TF group)<sup>9</sup>. Deaths were cardiac-related in 25.1 % of the cases, non cardiac in 49.2 % and unexplained in 27.7 %<sup>10</sup>. Moreover, the most frequent causes of non-cardiac death were pulmonary or renal disease, cancer, and stroke. Finally, multivariate analysis identified the EuroSCORE, renal failure, liver disease, and smoking as the most important predictors of mortality<sup>10</sup>. The FRANCE 2 registry included all the 3195 patients who were treated by TAVR in France from January 2010 to October 2011<sup>18</sup>. It is the largest registry carried out so far. The SAPIEN and CoreValve prostheses were used in 66.9 % and 33.1 % of the cases, respectively. Approaches were TF in 74.9 % of the cases, TS in 5.8 %, and TA in 17.8 %, while other routes (TAo or transcarotid) were used in 1.8 %. Procedural success was achieved in 96.9 % of cases<sup>18</sup>. Thirty-day and 1-year mortality rates were 9.7 % and 24.0 %, respectively. Furthermore, the rate of stroke at 1 year was 4.1%, while paravalvular aortic regurgitation was observed in 62.9 % of the patients (grade 1, 46.0 %; grade 2, 16.1 %; grade 3, 0.8 %) <sup>18</sup>. On multivariate analysis, a high EuroSCORE, a NYHA functional class III or IV, the use of the TA approach and a higher grade paravalvular aortic regurgitation were associated with a higher mortality<sup>18</sup>.

## PARTNER Study

The Placement Of Aortic Transcatheter Valves (PARTNER) study, which is the only randomized trial currently available, was conducted in 25 North American and 1 German centre using the Edwards SAPIEN Transcatheter Heart Valve (Edwards Lifesciences LLC, Irvine, CA)<sup>11,12</sup>. It provided the first evidence of the superiority of TAVI over medical treatment in inoperable patients, and of the non-inferiority in comparison to conventional surgery (SAVR) in high-risk patients. The trial included 1056 high-risk patients in 2 different cohorts: operable patients (cohort A) were randomized to TAVI (TF or TA according to their vascular access) versus conventional surgery (SAVR); inoperable patients (cohort B) were randomized to transfemoral TAVI versus medical treatment (including balloon aortic valvuloplasty). In the latter, TAVI was clearly superior to medical treatment, with an important reduction of all-cause mortality and hospitalizations<sup>11</sup>. One-year mortality was 30.7% in the TAVI group, versus 50.7 % in the medical group ( $P < 0.001$ )<sup>11</sup>. The rate of mortality continued to diverge with a 24.7% (43.3% compared to 68.0%) and 26.8% (54.1% compared to 80.9%) absolute reduction for the TAVI treated patients at 2 and 3 years post-implantation ( $p < 0.001$ ), respectively<sup>11</sup>. The number needed to treat was less than 4 patients. There was also significantly lower readmission rates for recurrent congestive heart failure (CHF), improved New York Heart Association functional class (75% vs. 42% NYHA class 1 or 2), and improved quality of life in TAVI treated patients compared to those treated with medical therapy<sup>11</sup>. In the high-risk group, TAVI was non-inferior to conventional surgery (SAVR) with regards to 1-year all-cause mortality (24.2 %, vs 26.8 %,  $P = 0.44$ )<sup>12</sup>. One-year stroke rate was 5.1 % in the TAVI group, vs

2.4 % in the SAVR group (P=0.07) and 30-day rate of major vascular complication was 11.0%, vs 3.2 % (P<0.001). Conversely, cases of serious haemorrhage were more frequent after SAVR (19.5 %, vs 9.3 %, P<0.001). A similar trend was recorded for new cases of atrial fibrillation (16 %, vs 8.6 %, P=0.006). These findings led the Food and Drug Administration to approve TAVI for inoperable patients in 2011 and more recently for high-risk patients in June 2012. The PARTNER trial was highly convincing but suffered from some potential bias incurred both in the intention-to-treat and as-treated analyses by including the fact that there were concomitant procedures performed in the surgical cohort in 40% of patients and there was a significant delay to treatment in 14% of the surgical patients<sup>11,12</sup>.

Table 2. Specific characteristics of Edwards Sapien 3 Valve

	23mm	26mm	29mm
Edwards esheath Introducer set (Transfemoral)	14F	14F	16F
Minimum Access Vessel Diameter	5.5mm	5.5mm	6.0mm
Edwards Certitude Sheath (Transapical)	18F	18F	21F
Native Annulus Size by TEE	18-22mm	21-25mm	24-28mm
Native Annulus Area	338-430mm	430-546mm	540-680mm
Area-derived diameter	20.7-23.4mm	23.4-26.4mm	26.2-29.5mm

## Structural Deterioration of Edwards SAPIEN Pericardial Valves

Structural valve deterioration (SVD) is a well-described complication with bioprosthetic valves. However, exactly as in patients who received standard pericardial valves through conventional open-heart procedures, patients subjected to TAVI are less exposed to the main cause of SVD which is tissue calcification, simply because this phenomenon occurs later in life and evolves much slower in old patients. TAVI has now reached a decade of clinical experience. Despite this, the long term durability of Edwards SAPIEN valves can not be known at this time as the follow-up is short. Two case studies have shown structural failure of Edwards SAPIEN XT valves at 1 and 3 years<sup>19,20</sup>. These first reports of SVD after TAVI may have important clinical implications. The common causes for SVD in bioprosthetic valves in the aortic position are: tissue calcification in 80% of cases, leaflet tears in 20% and occasionally pannus ingrowth<sup>19,20</sup>. It is believed that a similar pattern of SVD occurs in transcatheter bioprostheses; however, evidence is not yet available. Some of the TAVI prostheses, especially the Edwards SAPIEN XT valve consist of the same material as used for conventional stented pericardial valves, but in contrast to the no-touch technique in conventional pericardial valve operations, the preoperative crimping process may harm to a certain degree transcatheter valves. Crimping, however, is inevitable in order to be able to insert transcatheter valves through small-diameter sheaths. Currently, the only tissue tolerating crimping is pericardium, whilst porcine leaflets are not able to withstand crimping. The potential effect of crimping on the calcification, strength, and durability of the bioprosthesis, however, has never been evaluated in clinical practice.

In experimental rat models, precrimping of the SAPIEN valve seems to have no influence on the grade of calcification; however, it significantly influences the ultrastructure of the pericardial tissue<sup>21</sup>. To what extent these changes correlate with medium-term and long-term durability is unknown so far; however, the results of this study demonstrate that extensive precrimping should be avoided<sup>21</sup>. For the future, it will be interesting to examine the potential effect of even tighter crimping on durability. This will be of special clinical importance because smaller devices are being developed. There has been research aimed at using dry valves. This is achieved by using glutaraldehyde (GLX) for the fixation of pericardial leaflets of Edwards SAPIEN valves. Although there is a considerable interest and excitement in this area, there are no clinical data on the use of dry GLX treated valves on the durability of Edwards SAPIEN device at present.

## Future Trends of Edwards SAPIEN Valves

Currently, the use of TAVI is restricted to patients considered to be at high risk or to be unsuitable for open heart valve replacement. Other groups of patients may become candidates for the transcatheter technique and this possibility should be evaluated. Patients at intermediate risk represent a major question for the future. In clinical practice, a shift towards lower-risk populations was observed in the FRANCE 2 registry as well as in most European registries<sup>18</sup>. In the German registry, 16 % of indications for the use of TAVI were motivated by the wish of intermediate-risk patients<sup>22</sup>. However, before this trend becomes common practice, longer-term follow-up concerning the durability of the transcatheter heart valves is mandatory. Indeed, while case reports of transcatheter valve failure are anecdotic<sup>19,20</sup>, the current follow-up does not exceed 5 years and neither the time nor the modalities of prosthetic deterioration are known at present time. Two trials are underway to evaluate TAVI in the intermediate-risk patients. The PARTNER II trial, which will use the SAPIEN XT, will include patients with a surgical predicted mortality between 4 % and 10 %, according to the STS PROM<sup>23</sup>.

“Valve-in- valve” implantation is an attractive alternative to surgical reoperation in elderly patients with failed conventional bioprosthesis. The first results from simple clinical studies are promising<sup>24</sup>, but more information is needed in order to better determine the types of bioprostheses suitable for this intervention, as well as the additional risks related to the double valve implantation and the durability of transcatheter valves in this situation.

Bicuspid aortic valves represent a formal contraindication to TAVI due to the risk of prosthesis deformation and dysfunction. While the current literature on this matter is relatively scarce, the issue of treating this specific sub-group of patients will become more often considered as indications of TAVI are extended to younger and lower-risk patients.<sup>25</sup>

Multimodality imaging, with fusion imaging may play an important role for more consistent prosthesis delivery and accurate positioning. The use of the TF approach will become even more frequent with the miniaturization of the devices, resulting in a lower use of the alternative approaches.

New prostheses are on the horizon, most of them self expandable with attractive features such as repositionability and retrievability. The profile of the delivery systems will be reduced and will allow a TAVI procedures to be performed in catheterization laboratories, on conscious but lightly sedated patients, using percutaneous suture closure devices with reduction in ancillary costs and hospital lengths of stay.

Overall, the procedure will be simplified, with consequent reduction of the complication rate.

## Conclusion

Since the first use in 2002 by Cribier of a transcatheter aortic valve in patients, this technique (TAVI) using the Edwards SAPIEN pericardial valve configuration has been utilised in increasing numbers in many centres around the world. This device has been specifically utilised in patients of an advanced age and in frail physical condition in whom the conventional aortic valve replacement would carry a very high risk. However, more recently, with advances in the quality of the TAVI devices and following improved results due to greater experience in its manipulation and insertion, it is increasingly proposed that this technique could be used even in patients who may not represent a high risk for conventional aortic valve replacement.

The progressive increase in valve durability and the reduction of associated complications due to advances in the device delivery systems will ultimately determine the future of this novel type of treatment.

It is however reassuring to know that the concept of using glutaraldehyde-treated bovine pericardium, attached onto a flexible frame, has, under various configurations, traversed successfully more than forty years of clinical use.

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Chapter 4

# The Role of Echocardiography in the Evaluation of Bioprosthetic Valve Performance with an Emphasis on Pericardial Xenografts

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*We may think in generalities but we live in detail*

Lucian Blaga (1895 – 1961)

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## Introduction

Since their first introduction in the 1960's bioprosthetic heart valves have undergone multiple and various modifications. The porcine aortic valve 'per se' cannot be modified. Only the size, position and arrangement of its sewing rim have been altered, marginally improving its haemodynamic performance. Still, despite these modifications, porcine valves could not be used in small aortic annuli.

The pericardial valve, however, could be modified in various ways in order to improve its performance while retaining its excellent haemodynamic profile and its reduced risk of embolisation. The main modification made for the second generation of pericardial valves is the technique of mounting the pericardium onto the stent which reduced the risk of valve cusp abrasion.

Pericardial valves have shown a virtual absence of thrombotic valve obstruction and a lower risk of embolism even in the absence of anticoagulant treatment when compared with porcine valves. As a result the trend world-wide is towards a greater use of bioprosthesis and especially pericardial xenografts<sup>1</sup>. Pericardial heart valves are manufactured from glutaraldehyde-treated bovine pericardium attached onto a semi-flexible stent. They confer, despite the presence of the sewing rim, excellent haemodynamic characteristics. Porcine stentless aortic valves<sup>2</sup> are reported to be haemodynamically better than the stented variety, but the difficult and longer duration of the technique of their insertion, together with the less favourable long-term results limit their use to a small number of patients.

## Role of Echocardiography

Transthoracic echocardiography with Doppler assessment represents the optimal non-invasive method for assessment and follow-up after bioprosthetic valve implantation. Echocardiographic evaluation follows the same principles of assessment as those for native valves, although some important considerations exist which will be discussed in more detail.

## Timing of Studies

All patients should undergo a complete baseline echocardiographic assessment within twelve weeks of surgery. Ideally this study should be performed when the sternal wound has healed, ventricular function has stabilized, and any post-operative anaemia has resolved (given that these factors will impact on recorded transvalvular gradients). Not only does this initial study provide a reference for comparison for future studies with regards to transvalvular gradients, but also allows documentation of the presence or absence of transvalvular and paravalvular regurgitation and any element of patient-prosthesis mismatch.

In the absence of any clinical signs or symptoms suggestive of valvular dysfunction, routine echocardiography in the first few years post-implant is not normally indicated after this baseline assessment. Annual echocardiography is recommended after the fifth year in patients with a bioprosthesis, and earlier in patients of a young age at time of valve replacement<sup>3</sup>.

## Key Information Central to the Interpretation of Echocardiographic Findings

Several key pieces of information are essential prior to performing an echocardiogram for the assessment of bioprosthetic valve function:

### Year of implant

**Valve type and size** – essential in the interpretation of transvalvular gradients and effective orifice area. A large body of data exists regarding normal ranges for transvalvular velocities, gradients, and effective orifice area for bioprosthesis in both the aortic and mitral positions.

**Patient body surface area (BSA)** – assess whether patient–prosthesis mismatch is present and to interpret cardiac chamber size.

**Blood pressure and heart rate** – transvalvular velocities and gradients are flow-dependent, and in particular the mean gradient across a mitral prosthesis is highly dependent on the duration of the diastolic filling period. The degree of both mitral and aortic regurgitation can be underestimated in the presence of hypotension.

## Assessment of Bioprosthetic Function

Echocardiographic assessment should follow the same principles as those for the assessment of native valve function. The following factors should be assessed individually:

### Leaflet morphology and mobility

The leaflets of a normally functioning pericardial bioprosthesis should appear thin, with unrestricted leaflet excursion and no evidence of prolapse. The stentless valves may appear indistinguishable from a native valve, whilst the struts of a stented valve are easily identifiable (Figure 1). Any evidence of leaflet thickening, calcification, or restricted/excessive leaflet mobility should be documented.

### Aortic root and sewing ring motion

The valve should appear well-seated with no evidence of rocking motion during the cardiac cycle. Regions of separation from the native annulus should be documented. Colour Doppler imaging allows identification of paravalvular regurgitation. The presence of rocking motion of a bioprosthesis in the aortic position is a sign of a large dehiscence<sup>4</sup>, whereas increased mobility can be seen in a normally functioning mitral bioprosthesis secondary to retention of the posterior or both anterior and posterior native valve leaflets. In this case the absence of a regurgitant jet allows differentiating from dehiscence of the sewing ring. Aortic root thickening may be noted early after implantation of a stentless bioprosthesis, and typically represents haematoma and oedema. This appearance typically diminishes 3 to 6 months after surgery, and can often be mistaken for aortic root abscess. Appearances should be compared with the intraoperative and early post-operative studies.

### Measurement of transvalvular velocity, gradient, and effective orifice area (EOA)

As with the assessment of native valves, colour Doppler, pulsed-wave (PW) and continuous wave (CW) Doppler are utilised to interrogate valve function from several acoustic windows. Transvalvular velocities and gradients are determined by several factors, and are dependent of prosthesis type, size, and flow across the valve.

### Aortic bioprostheses

For valves in the aortic position, assessment should be made of peak velocity, peak and mean transvalvular gradients, and the effective orifice area (EOA – derived from the continuity equation)<sup>5</sup>.

Both peak velocity and peak and mean gradients are flow-dependent, and high velocities and gradients may be recorded in a normally functioning prosthesis in the setting of increased transvalvular flow (anaemia or high cardiac output state). Calculation of the EOA allows a more accurate assessment of valve function than transvalvular gradients alone. The EOA is dependent on the size of the valve implanted, and should therefore be referenced to the specific valve type and size. Importantly, the LVOT dimension cannot be substituted in the continuity equation by the labelled prosthesis size, as this will yield an overestimation of valve area<sup>6</sup>. The Doppler velocity index (DVI) is helpful to assess prosthetic valve function, given that it avoids measurement of the left ventricular outflow tract (a common cause of erroneous results) and provides a flow-independent assessment of valve function. The DVI is determined by the ratio of the velocity proximal to aortic valve (in the LVOT) to the velocity through the prosthesis.

### Mitral bioprostheses

In mitral bioprosthetic valves, measurements should be made of peak velocity, mean gradients, and EOA. Unlike the assessment of native mitral valve area, the EOA in mitral bioprostheses should be obtained by means of the continuity equation (utilising the stroke volume measured in the LVOT) rather by utilisation of the pressure half-time method<sup>7</sup>.

Published reference values for peak velocities, peak and mean gradients and effective orifice areas for aortic and mitral pericardial bioprostheses are available for individual valve models and sizes<sup>8</sup>.

### Indirect measures of bioprosthesis function

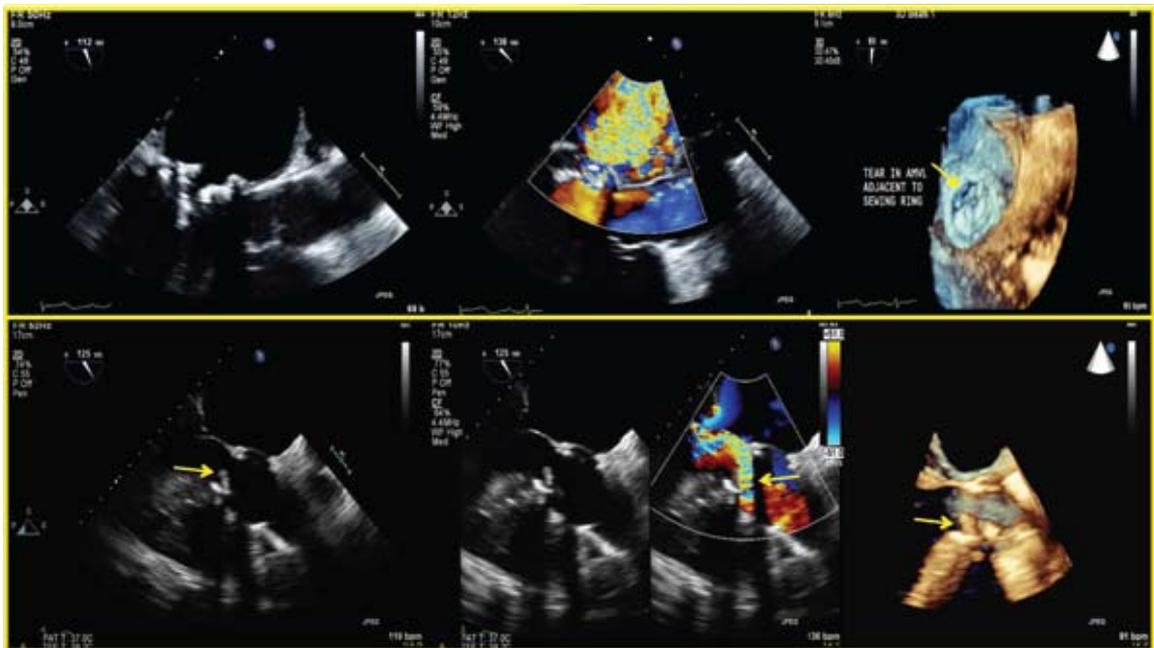
Indirect markers of bioprosthetic valve dysfunction should be sought on echocardiography, with particular reference to changes over time. Left ventricular size, function, and the presence of left ventricular hypertrophy are particularly pertinent in patient with an aortic bioprosthesis. In patients with mitral bioprostheses, assessment of left ventricular size and function, left atrial size, pulmonary artery pressures, and right heart size and function should be made<sup>8</sup>.



Figure 1: Normal Echocardiographic Appearances

*Left: The leaflets of a normally functioning pericardial aortic bioprosthesis are shown in the mid-oesophageal long-axis and short-axis views on TOE in a patient with a Hemashield aortic root and a 25mm Perimount valve. The valve sewing ring and stents are clearly seen, with the leaflets appearing thin, with no evidence of thickening, calcification or prolapse.*

*Right: A normally functioning mitral bioprosthesis is shown in the parasternal long-axis view on TOE in a patient with a 27mm mitral bioprosthesis. The valve stents are clearly seen, but the leaflets are not easily visualised due to shadowing.*



*Figure 2: Structural Valve Deterioration*

*Upper panel: Structural valve deterioration with leaflet thickening and calcification in a 27mm mitral bioprosthesis. Severe transvalvular mitral regurgitation is noted, filling a significant area of the left atrium. On 3D imaging a tear in the leaflet is noted adjacent to the sewing ring.*

*Lower panel: Structural valve deterioration with a leaflet tear in a 29mm aortic bioprosthesis on both 2D and 3D imaging. Severe eccentric transvalvular aortic regurgitation is demonstrated, with the jet being directed posteriorly onto the anterior mitral valve leaflet.*

## The Role Of Various Echocardiographic Imaging Modalities in the Assessment of Bioprosthetic Valves

### Transthoracic Versus Transoesophageal Echocardiography

Given that acoustic shadowing is less of an issue in bioprosthetic valves than mechanical valves, transthoracic echocardiography (TTE) is the first-line investigation for assessment and follow-up of valve function. However, transoesophageal echocardiography (TOE) provides superior image quality for the assessment of bioprosthetic leaflet morphology and mobility and identification of cusp calcification and thickening in cases of suspected prosthetic valve dysfunction. In addition, more accurate localisation and quantification of valvular regurgitation can be made. TOE plays a key role in the management of patients with suspected prosthetic valve endocarditis, in particular for the identification of abscess formation or new paravalvular regurgitation.

### The Role of Stress Echocardiography

Stress echocardiography can provide useful information in patients in whom there is discordance between reported symptoms and resting haemodynamic and Doppler parameters, as well as in patients who deny symptoms despite evidence of prosthetic valve dysfunction. In these “asymptomatic” patients symptoms may be unmasked during exercise testing.

Prosthetic valve stenosis or significant patient-prosthesis mismatch (PPM) is generally associated with a substantial increase in mean gradients and pulmonary artery systolic pressure and a significant

impairment of exercise capacity on exercise echocardiography<sup>9</sup>. An increase in mean transvalvular gradient of >20mmHg for aortic or >12mmHg for mitral bioprostheses respectively is indicative of severe bioprosthesis dysfunction or PPM<sup>9</sup>. High resting and exercise gradients are more frequently observed in smaller bioprosthesis (<21mm in the aortic position and <25mm in the mitral position).

## Long-Term Complications and the Role of Echocardiography in Identification and Management

### 1 Structural Valve Deterioration

In contrast with mechanical prostheses which have excellent durability (especially contemporary models), bioprosthetic valves are subject to structural valve deterioration (SVD)<sup>10</sup>. Both porcine aortic and bovine pericardial valves are exposed, with the passage of time, to tissue degeneration.

The 'so-called' advances in tissue fixation and the treatment with 'anti-calcification' processes have not shown their efficacy whatsoever. There is no known published scientific evidence that these chemical interventions have either increased valve durability or improved patient survival.

What is clearly documented is that pericardial bioprosthesis have better durability when inserted in the aortic as compared with the mitral position<sup>11</sup> and that pericardial bioprosthesis have a lower rate of SVD than the porcine aortic valves in both the aortic<sup>12,13</sup> and the mitral position<sup>13</sup>.

Structural valve deterioration is a result of tissue calcification in over 75% of cases, valve leaflet tears in 20%, and fibrosis/calcification in 5%. Neither of these pathological processes produce sudden unexpected valve failure if patients are correctly followed up.

The risk of SVD increases over time, and can result in either valve stenosis, regurgitation, or both (Figure 2). Primary valve failure secondary to SVD occurs in 3-4% of implanted bioprosthesis within 5 years, and in up to 35% of valves within 15 years of implantation. The durability of pericardial bioprosthesis depends on multiple factors, most importantly the environment into which the valve is implanted. Several risk factors for SVD have been identified, including younger age at valve implantation, a bioprostheses in the mitral position, the presence of chronic renal impairment, and hyperparathyroidism<sup>14-16</sup>. In addition, for bioprostheses in the aortic position, factors such as systemic hypertension, left ventricular hypertrophy, and poor LV function, and bioprostheses size relate to the development of SVD<sup>15</sup>. In particular, age at implantation remains the most important determinant of valve calcification and SVD, with freedom from reoperation due to SVD at 15 years of over 99% in patients over 75 years of age, compared with 35% in patients below the age of 65 years<sup>10</sup>.



### 2 Stent Creep

Stent creep represents an uncommon form of structural valve degeneration. Stent creep refers to the progressive and permanent inward deflection of the valve stents posts away from their usual vertical orientation. It is a multifactorial process, and may be related to flexibility of the stent posts, stent material fatigue, inward pressure from leaflet closure, and outward pressure from oversizing of the valve. Ultimately this bowing down of the stents into the central orifice will lead to a reduction in the area for blood flow and stenosis (Figure 3).

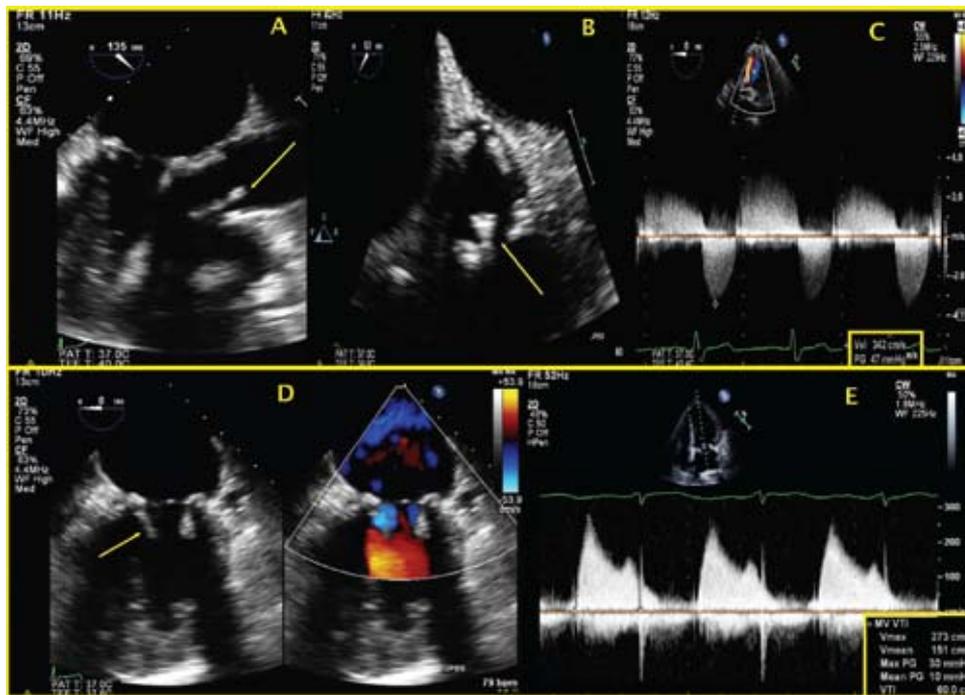


Figure 3: Stent Creep

Upper panel: Stent creep in a 21mm aortic bioprosthesis, demonstrating the inward deflection of the stent post most noticeable in the region of the right coronary sinus (A and B). Increased transvalvular velocity (3.4cm/sec) and gradients (47mmHg) are demonstrated from the deep transgastric view (C).

Lower panel: Stent creep in a ..... mitral bioprosthesis, again demonstrating inward deflection of the stent post adjacent to the LLVOT(D) with an associated increase in transvalvular velocities and gradient (E).

### 3. Patient-Prosthesis Mismatch

Patient-prosthesis mismatch (PPM) does not represent intrinsic dysfunction of a bioprosthesis, but rather refers to the situation wherein the effective orifice area of a normally functioning prosthesis is too small in relation to the patient’s body size and cardiac output requirements<sup>17</sup>. TTE is essential to differentiate between these two situations. The hallmark of PPM is the identification of high transvalvular gradients post-operatively. While moderate PPM may be quite common in bioprostheses in both the aortic and mitral positions, severe PPM is less frequent, occurring in up to 10% of prosthesis (regardless of position)<sup>18</sup>. PPM can largely be predicted and prevented at the time of operation by knowledge of the anticipated effective orifice area of the valve type and size to be implanted from published reference values. The presence of PPM is associated not only with less favourable haemodynamics<sup>19</sup>, but also with a greater risk of adverse cardiac events and reduced survival. PPM in an aortic prosthesis results in less regression of left ventricular hypertrophy<sup>20</sup> and less improvement in functional class post-operatively<sup>19</sup>, whereas PPM in a mitral prosthesis results in persistent pulmonary hypertension<sup>21</sup>, atrial fibrillation, and right ventricular dysfunction. PPM has a greater impact on outcomes in those patients undergoing valve replacement at a younger age, and in the presence of left ventricular hypertrophy or poor left ventricular function.



The indexed effective orifice area is the most widely validated method for identifying the presence of PPM. The calculated EOA (derived from the continuity equation) is indexed to the patient’s body surface area. Cut-offs used to identify the presence and severity of PPM for prostheses in both the aortic and mitral position are shown in Table 1.

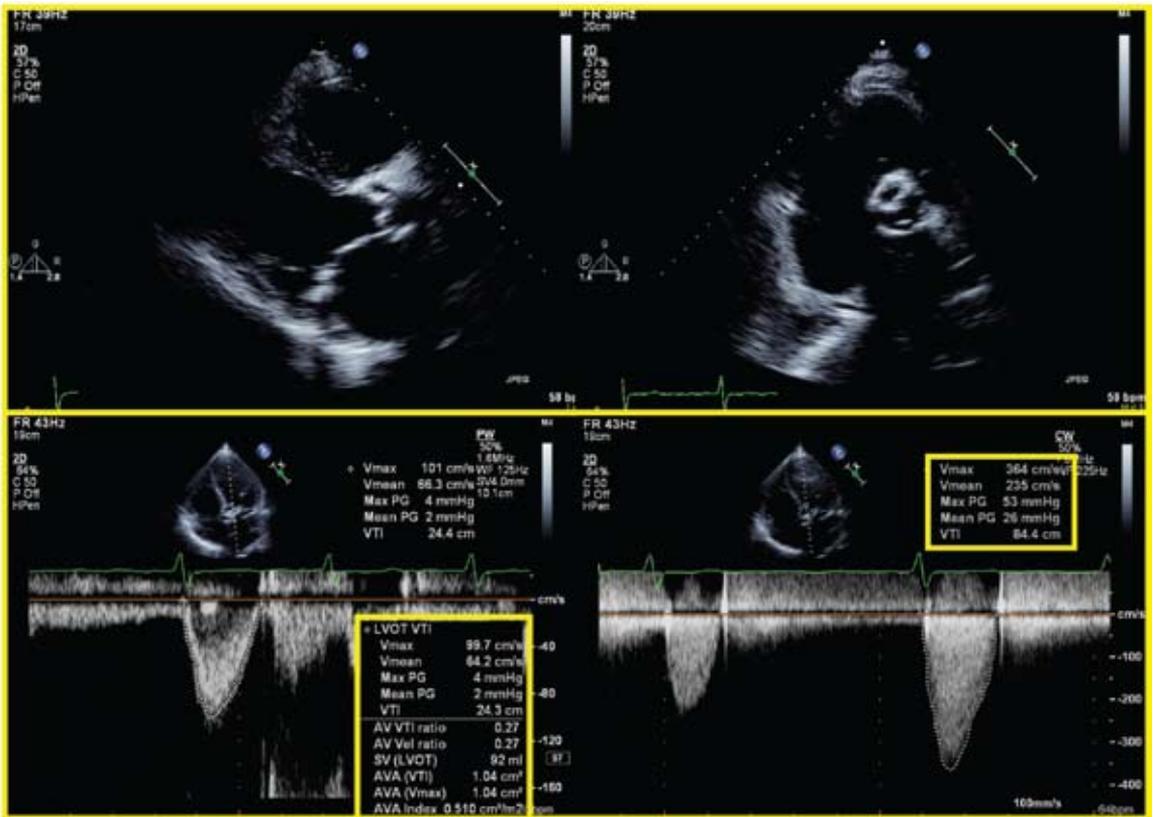


Figure 4: Valvular Stenosis

Upper panel: Structural valve deterioration in a 25mm Carpentier Edwards Perimount aortic bioprosthesis, with leaflet thickening and restriction seen in both the parasternal long-axis and short-axis views on transthoracic echocardiography.

Lower panel: Significant stenosis is noted, with an increase in transvalvular velocities (3.6m/s) and mean gradient (26mmHg). The aortic valve area is calculated at 1.04cm<sup>2</sup> (indexed to 0.51cm<sup>2</sup>/m<sup>2</sup>), with a Doppler velocity index of 0.27. There parameters are consistent with borderline severe aortic stenosis.

Table 1. Criteria for the Diagnosis and Quantification of Patient-Prosthesis Mismatch by means of Indexed Prosthetic Effective Orifice Area

Position	Mild (cm <sup>2</sup> /m <sup>2</sup> )	Moderate (cm <sup>2</sup> /m <sup>2</sup> )	Severe (cm <sup>2</sup> /m <sup>2</sup> )
Aortic	>0.85	≤0.85	≤0.65
Mitral	>1.2	≤1.2	≤0.9

#### 4. Valve Stenosis

The initial presentation of prosthetic valve stenosis may be the incidental finding of elevated transvalvular velocities and gradients on echocardiography. Prosthetic valve stenosis is typically associated with abnormal leaflet morphology and mobility, with evidence of leaflet thickening and/or calcification (Figure 4). Prosthetic valve stenosis is usually associated with high transvalvular velocities and gradients, although this is not definitive evidence of intrinsic valve dysfunction and these findings can be seen in patient-prosthesis mismatch, high-output conditions, and with significant valvular regurgitation. Conversely, velocities and gradients may be seen in a valve with

significant stenosis in the setting of poor left ventricular function or a low-output state.

For valves in the aortic position, the Doppler velocity profile and acceleration time are useful adjuncts to transvalvular velocities and gradients in distinguishing intrinsic stenosis. A more rounded contour, with peak velocity occurring in mid-ejection and an associated increase in acceleration time, is seen in cases of valvular stenosis. As discussed earlier, the effective orifice area and Doppler velocity index are less flow-dependent and should be calculated as a routine in patients with a bioprosthetic valve. For valves in the mitral position, the mean transvalvular gradient should always be interpreted in the setting of the heart rate. The criteria used to identify and quantify prosthetic valve stenosis are shown in Table 2.

While structural valve deterioration is the most common cause of bioprosthetic valve stenosis, the differential diagnosis includes pannus, thrombus, and infective endocarditis. Pannus formation results from the ingrowth of fibrous tissue, often leading to slowly progressive obstruction. It may be difficult to distinguish from thrombus, and the two processes may coexist in the same patient.

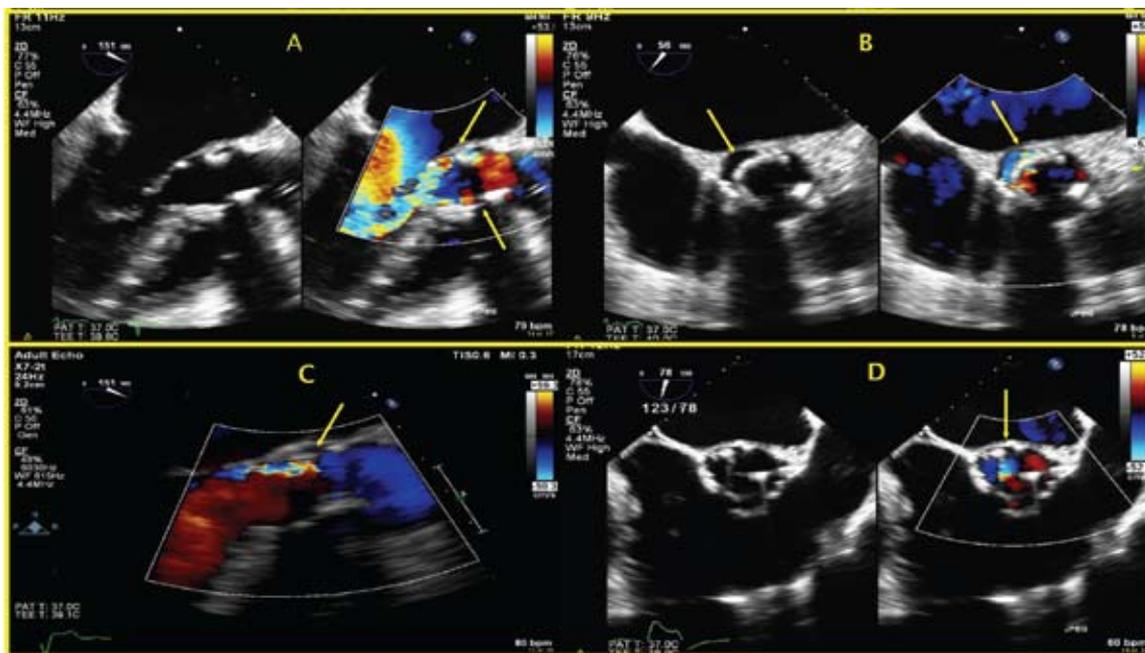


Figure 5: Valvular Regurgitation

Upper panel: The mid-oesophageal long-axis view on TOE (A) demonstrates the presence of two paravalvular leaks arising outside of the sewing ring in an anterior and posterior position in a patient with a Carpentier Edwards Perimount aortic bioprosthesis. A short-axis view of the aortic valve confirms the presence of an echo lucent space in the 9 o'clock to 12 o'clock position between the sewing ring and the native annulus. Colour flow imaging demonstrates evidence of colour flow in this region consistent with the presence of a paravalvular leak.

Lower panel: The mid-oesophageal long-axis view on TOE (C) demonstrates the presence of transvalvular regurgitation, with the colour jet clearly arising within the sewing ring of the aortic bioprosthesis. A short-axis view of the aortic valve (D) confirms that the colour jet is transvalvular rather than paravalvular in origin.

Thrombus is more prevalent in mechanical than bioprosthetic prostheses, often occurring in patients with subtherapeutic level of anticoagulation. In patients with a bioprosthesis, thrombus is seen most commonly in the early post-operative period, particularly in patients with a mitral prosthesis, severe left ventricular dysfunction, atrial fibrillation, or a history of thrombosis or embolism. TOE is required to help differentiate between thrombus (often larger, more mobile, and with a softer ultrasound density) and pannus.

Table 2. Criteria for the Identification and Quantification of Prosthetic Valve Stenosis

	Aortic Position			Mitral Position		
	Normal	Possible Stenosis	Significant Stenosis	Normal	Possible Stenosis	Significant Stenosis
Valve Morphology and Leaflet Mobility	Normal	Often abnormal Leaflet thickening/ calcification Pannus/ thrombus	Abnormal Leaflet thickening/ calcification Pannus/ thrombus	Normal	Often abnormal Leaflet thickening/ calcification Pannus/ thrombus	Abnormal Leaflet thickening/ calcification Pannus/ thrombus
Peak velocity (m/s)	<3	3-4	>4	<1.9	1.9-2.5	>2.5
Mean gradient (mmHg)	<20	20-35	>35	≤5	6-10	≥10
Doppler velocity index (DVI)	≥0.3	0.25-0.29	<0.25	<2.2	2.2-2.5	>2.5
Effective orifice area (cm <sup>2</sup> )	>1.2	0.8-1.2	<0.8	≥2	1-2	<1
Jet contour	Triangular, early peaking	Triangular to intermediate	Rounded, symmetric	-	-	-
Acceleration time (ms)	<80	80-100	>100	-	-	-
Pressure half-time (ms)	-	-	-	<130	130-200	>200

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## THE PERICARDIAL HEART VALVE

Table 3. Criteria for the Identification and Quantification of Prosthetic Valve Regurgitation

	Aortic Position			Mitral Position		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Valve Morphology and Leaflet Mobility	Usually normal	Usually abnormal Leaflet thickening/ calcification Leaflet prolapse Dehiscence or rocking	Usually abnormal Leaflet thickening/ calcification Leaflet prolapse Dehiscence or rocking	Usually normal	Usually abnormal Leaflet thickening/ calcification Leaflet prolapse Dehiscence or rocking	Usually abnormal Leaflet thickening/ calcification Leaflet prolapse Dehiscence or rocking
Jet width in central jets (%LVOT diameter)	Narrow $\leq 25\%$	Intermediate 26-64%	Large $>65\%$	-	-	-
Jet area	-	-	-	Small central jet $<4\text{cm}^2$ or $<20\%$ of LA	Variable	Large central jet $>8\text{cm}^2$ or $>40\%$ of LA Variable size in wall hugging jet
Flow convergence	-	-	-	None or minimal	Intermediate	Large
Jet density	Incomplete or faint	Dense	Dense	Incomplete or faint	Dense	Dense
Jet deceleration rate (PHT, ms)	Slow $>500$	Variable 200-500	Steep $<200$			
Vena contracta (mm)	$<3$	3-6	$>6$	$<3$	3-6	$>6$
Regurgitant volume (ml)	$<30$	30-59	$\geq 60$	$<30$	30-59	$\geq 60$
Regurgitant fraction (%)	$<30$	30-49	$\geq 50$	$<30$	30-49	$\geq 50$
EROA ( $\text{mm}^2$ )	-	-	$>30$	$<20$	20-39	$\geq 40$
Doppler velocity index	-	-	-	$<2.2$	2.2-2.5	$>2.5$

Circumferential extent of paravalvular leak	<10%	10-20%	>20%	-	-	-
Effect on cardiac chambers	-	-	Dilated LV	-	-	Dilated LA Dilated LA
Other	-	-	Prominent holo-diastolic flow reversal	-	-	Pulmonary hypertension Pulmonary vein systolic flow reversal

*Adapted in part from Otto C.: The Practice of Clinical Echocardiography 2012 4th Ed Chapter 25 (with permission of Elsevier).*

## 5. Valve Regurgitation

Although the echocardiographic assessment of valvular regurgitation follows similar principles as in patients with their native valves, it is important to distinguish physiologic from pathologic prosthesis regurgitation. TTE provides good visualisation of the left ventricular outflow tract, and acoustic shadowing is less of an issue in the aortic compared with the mitral position.

Physiologic regurgitation of bioprostheses typically takes the form of a small, transient central jet at the closure line of the leaflets. Pathological transvalvular regurgitation more commonly affects bioprostheses compared to mechanical valves. It usually occurs due to SVD such as leaflet tears, leaflet thickening, calcification, fibrosis or perforation but may also occur secondary to endocarditis, thrombus or pannus. In these cases, TOE is particularly helpful in assessing leaflet morphology and mobility and to determine the aetiology of the prosthesis regurgitation (Figure 5).

Paravalvular regurgitation occurs due to an incomplete seal between the prosthetic sewing ring and the native valve annulus, resulting in a regurgitant jet which arises outside of the sewing ring. Potential causes include heavy native annular calcification and fibrosis, a small implant size, suture dehiscence or endocarditis.

In the case of aortic prosthesis, the circumferential extent of a paravalvular leak gives an indication of its severity. A jet affecting >20% of the circumference of the sewing ring is indicative of severe PVR. A rocking motion of the valve is typically noted when > 40% of the sewing ring is dehisced. The majority of cases of PVR are clinically and haemodynamically insignificant. However, in the presence of breathlessness, heart failure, progressive left ventricular dilatation and impairment or haemolysis either percutaneous closure or redo surgery should be considered.



In addition to assessment of valve anatomy and leaflet morphology by 2D and 3D echocardiography both on TTE and TOE, there are numerous qualitative, semi-quantitative and quantitative measures that help to define the severity of regurgitation. In addition, indirect measures of severity, such as the effect of the regurgitant jet on the cardiac chambers and pulmonary pressures, provide useful adjunct information. The criteria used to identify and quantify prosthetic valve regurgitation are shown in Table 3.



Figure 6: Prosthetic Valve Endocarditis

Upper panel: The mid-oesophageal long-axis view on TOE demonstrates the presence of a large multilobular echogenic mass in the left ventricular outflow tract which is attached to the ventricular side of an aortic bioprosthesis.

Lower panel: A short-axis view of the aortic valve on TOE demonstrates the presence of an echo lucent space which is largest in the region of the non and right coronary sinuses in a patient with a 25mm Perimount Magna Ease aortic bioprosthesis. This patient had evidence of aortic root abscess formation and dehiscence of the sewing ring of the aortic valve with severe paravalvular regurgitation.

## 6. Endocarditis

Prosthetic valve endocarditis (PVE) occurs in 1-6% of patients, accounting for up to one third of all cases of infective endocarditis<sup>22</sup>. Both mechanical and bioprosthetic valves are equally susceptible to infection. In contrast to mechanical PVE, in which the infection is typically perivalvular (resulting in abscess formation, dehiscence, paravalvular regurgitation, pseudoaneurysms and fistulae), bioprosthetic valve endocarditis typically causes leaflet tears, perforations, and vegetations<sup>23</sup> (Figure 6). While the usual consequence of bioprosthetic valve endocarditis is heart failure secondary to new valvular regurgitation, valve stenosis can occur due to cusp thickening and the presence of a large vegetation.

While Doppler echocardiographic techniques can evaluate the haemodynamic consequences of PVE, TOE should be performed in addition to TTE in all cases of suspected PVE in order to identify the underlying anatomic lesions, assess valve morphology, and identify indications for surgery. TOE has superior sensitivity and specificity for the detection of vegetations, abscess formation, and perivalvular complications compared with TTE<sup>24</sup>. It is important to note, however, that the presence of intracardiac prosthetic material can hinder the identification of abscess formation and vegetations,

and hence a negative TOE is not uncommon and does not definitively exclude a diagnosis of PVE. In cases where clinical suspicion is high, a repeat examination may be indicated. PVE should be suspected in any case of a new dehiscence of a prosthetic valve or the presence of new paravalvular regurgitation, even in the absence of abscess formation or a vegetation<sup>25</sup>. TOE is particularly more sensitive than TTE in the case of PVE of a mitral prosthesis.

### Echocardiographic pitfalls in PVE

- A negative TTE and TOE does not exclude PVE.
- It may be difficult to differentiate between thrombus or strand and a vegetation.
- Aortic root thickening may be noted early after implantation of a stentless bioprosthesis, and typically represents haematoma and oedema.
- This appearance typically diminishes 3 to 6 months after surgery, and can often be mistaken for aortic root abscess.
- Increased mobility of the bioprosthetic sewing ring can be seen in a normally functioning mitral bioprosthesis secondary to retention of the posterior  $\pm$  anterior native valve leaflets. The absence of a paravalvular regurgitant jet allows differentiation from dehiscence of the sewing ring.

### Conclusion

Doppler echocardiography remains the first-line investigation of choice for the long-term follow up of patients after valve replacement. A comprehensive approach that incorporates the use of Doppler, colour flow, 2D and 3D imaging on both TTE and TOE will ultimately provide accurate assessment of bioprosthetic valve function and identify both the presence and often the cause of valve dysfunction.

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## Chapter 5

# Innovative statistical methods which can be used to predict the performance of pericardial valves and patient related outcomes over time

*M Mostafa Mokhles and Johanna JM Takkenberg*

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*Despite the contrary belief, truth is often made of several veiled contradictions and even abstract science relies at times on paradoxes.*

Bertrand Arthur William Russell (1872-1970)

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## Introduction

Outcome research is essential in providing evidence-based health care and the statistical analyses of outcome research is an important methodological issue. Although randomized trial designs are considered the ‘gold standard’, the empirical basis of outcomes research is mainly based on observational studies. The correct analyses of data gathered in observational studies can, however, be a challenging process. Standard survival analysis methods, such as Kaplan Meier curves, log-rank test and Cox proportional hazard model, are widely accepted tools in outcome research. However, in many instances these methods are not sufficient for correct statistical analysis of available data. This chapter will provide an overview of several innovative statistical methods which have been developed during the past decades and which enable researchers and clinicians to appropriately deal with the huge amount of data gathered in clinical studies of patients receiving artificial heart valves. A special emphasis is placed on the application of modern statistical methods to the performance of pericardial heart valves, created and used for the first time in 1971 in Great Britain. The following innovative statistical methods will be discussed in this chapter: microsimulation models for outcome prediction, competing risks and patient outcome, assessment of valve performance over time, and joint modeling.

## Microsimulation models for outcome prediction

Most widely used models for predicting patient outcome are currently mainly based on logistic regression, Cox regression and simulation models. While logistic regression and Cox regression are predominantly used for predicting patient outcome on short and intermediate term, respectively, simulation models can be used for predicting long-term outcomes. This makes simulation models particularly suitable for predicting the long-term outcome of patients receiving pericardial valves. Simulation entails the process of imitating a certain situation with a set of mathematical formulae. Currently, mainly two types of simulation models are used in health care research: Markov state-transition model and microsimulation model. Although these models have similar basic assumptions, there are some important differences between these two types of simulation models. While the Markov model simulates the outcome of a virtual patient population over time (at ‘macro’ level), the microsimulation allows to simulate the lives of individual patients (at ‘micro’ level). In addition, in Markov models the follow-up time is divided in different intervals during which events may or may not occur, while in microsimulation the time to next event is estimated based on the probability distribution of that event. Furthermore, Markov model has “no memory” assuming that subjects in a particular state are a homogeneous group without variability, while microsimulation models are capable of adjusting hazard for the individual patient depending on the prior events<sup>1</sup>. For these reasons, microsimulation is at the moment the most suitable simulation model for prediction of patient-specific outcome after cardiac valve replacement.

Microsimulation is a general term for modelling the behavior and interactions of micro units. Microsimulation methodologies have been developed in the field of operational research and are mainly used in disease screening programs, health economics for estimating the health consequences and economic costs of different clinical strategies in a population of interest, and sporadically in clinical studies<sup>2-7</sup>. An important advantage of these models is that it allows to investigate alternative clinical strategies in a population of interest and to take into account variability among subjects.

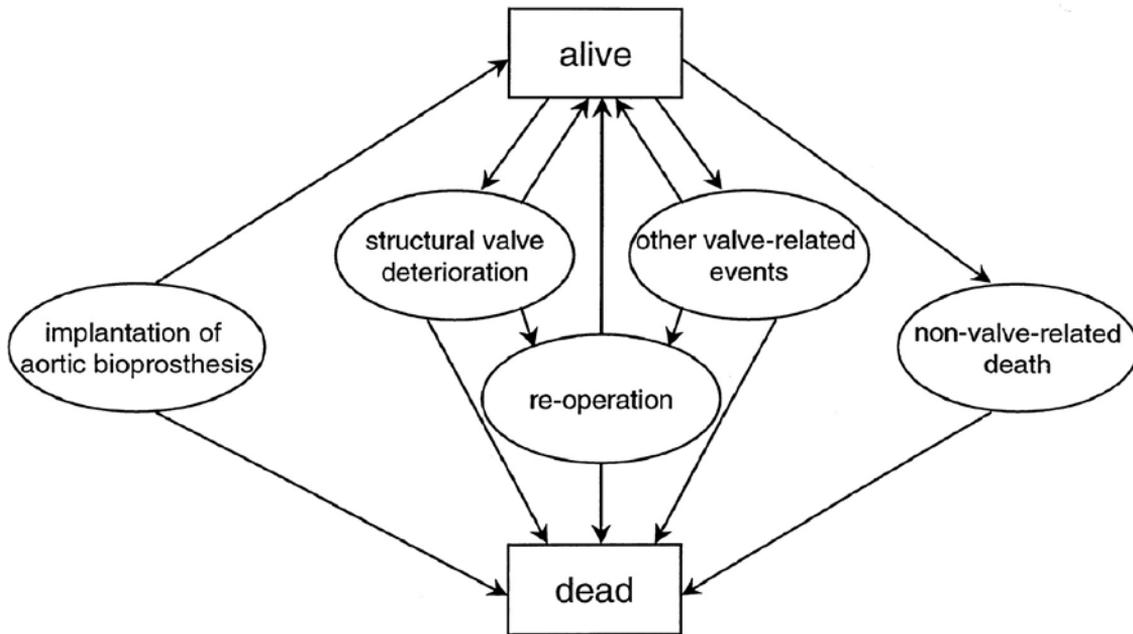


Figure 1: Structure of microsimulation model. After implantation of bioprosthesis, valve-related events can occur, which can lead to reoperation and mortality. Non-valve-related death indicates background mortality.

From: Puvimanasinghe JP, Steyerberg EW, Takkenberg JJ, Eijkemans MJ, van Henverden LA, Bogers AJ, et al. Prognosis after aortic valve replacement with a bioprosthesis: predictions based on meta-analysis and microsimulation. *Circulation*. 2001;103(11):1535-41.

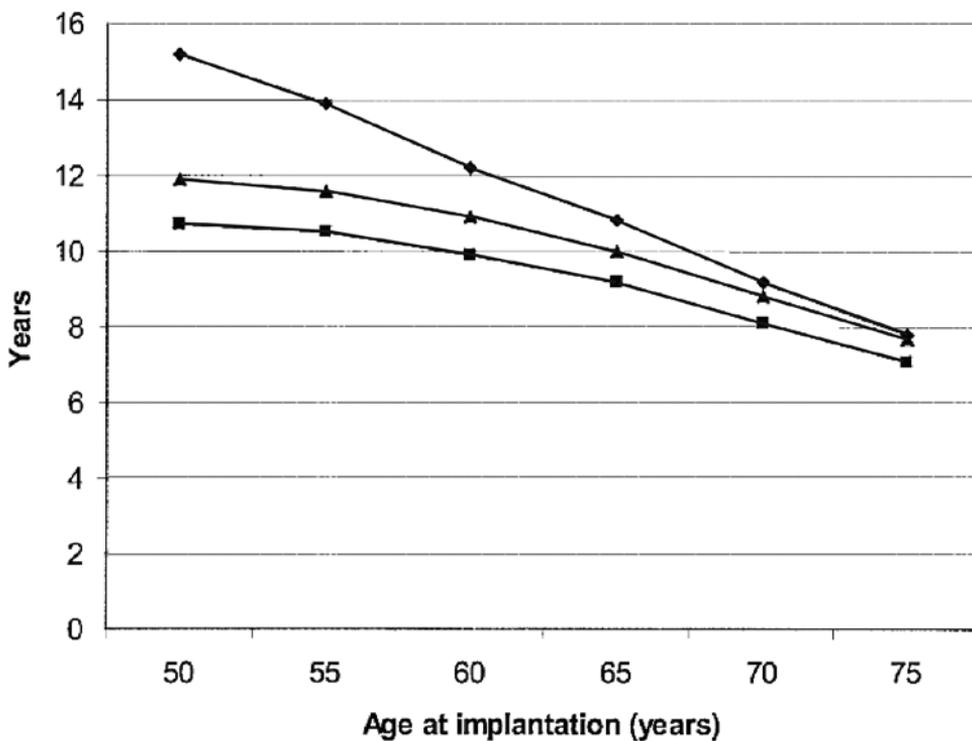


Figure 2: Life expectancy, reoperation-free life expectancy and event-free life expectancy after CE pericardial valve implantation

From: Puvimanasinghe JP, Takkenberg JJ, Eijkemans MJ, Steyerberg EW, van Henverden LA, Grunkemeier GL, et al. Prognosis after aortic valve replacement with the Carpentier-Edwards pericardial valve: use of microsimulation. *Ann Thorac Surg*. 2005;80(3):825-31.

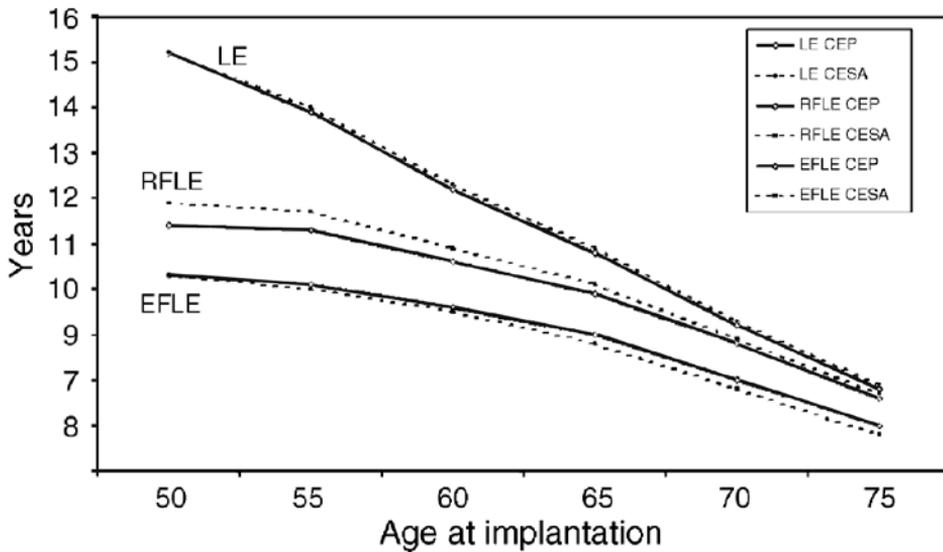


Figure 3: Life expectancy (LE), reoperation-free life expectancy (RFLE) and event-free life expectancy (EFLE) after AVR with Carpentier-Edwards pericardial (CEP) and Carpentier-Edwards supraannular (CESA) bioprostheses. From: Puvimanasinghe JP, Takkenberg JJ, Eijkemans MJ, van Herwerden LA, Jamieson WR, Grunkemeier GL, et al. Comparison of Carpentier-Edwards pericardial and supraannular bioprostheses in aortic valve replacement. *Eur J Cardiothorac Surg.* 2006;29(3):374-9.

Microsimulation can be best compared with a simulation program of a flight simulator used in the aviation industry which simulates a particular flight taking into account how the aircraft reacts to applications of flight controls, air density, turbulence, wind shear, cloud and other relevant variables<sup>3</sup>. In health care, this means that evidence obtained from the clinical practice is used to supply the model with information and to make predictions with regard to patient outcome based on this information. Figure 1 shows, for example, the structure of a microsimulation model for patients receiving a pericardial bioprosthesis<sup>8</sup>. Microsimulation simulates the lives of these patients taking into account several valve-related events (e.g. failure, reoperation, endocarditis) that may occur during the remaining life expectancy<sup>3</sup>. If microsimulation of a particular patient is repeated numerous times, a “virtual” patient population is created, consisting of patients with identical characteristics and with all possible outcomes that these patients can experience. This is the main power of microsimulation; the model is able to simulate individual life histories of numerous virtual patients with the same characteristics. The obtained information from the model provides insight into all probable outcomes for that particular patient and the importance of the individual-related events. The model also takes into account the morbidity and mortality that the patient may experience according to predefined estimates of operative mortality, event occurrence and their consequences (e.g. death, reoperation), and the probability of dying of other non-valve-related causes. A typical run would be for 10,000 to 1,000,000 individuals. From this large dataset with identical patients the average prognosis of an individual patient with those characteristics can be calculated<sup>3</sup>.



Puvimanasinghe and colleagues used the microsimulation model to provide insight into the age- and sex-related life expectancy and lifetime risks of valve-related events after aortic valve replacement (AVR) with the Carpentier-Edwards (CE) pericardial valve<sup>9</sup>. Figure 2 shows the life expectancy, reoperation-free life expectancy and event-free life expectancy of patients receiving a

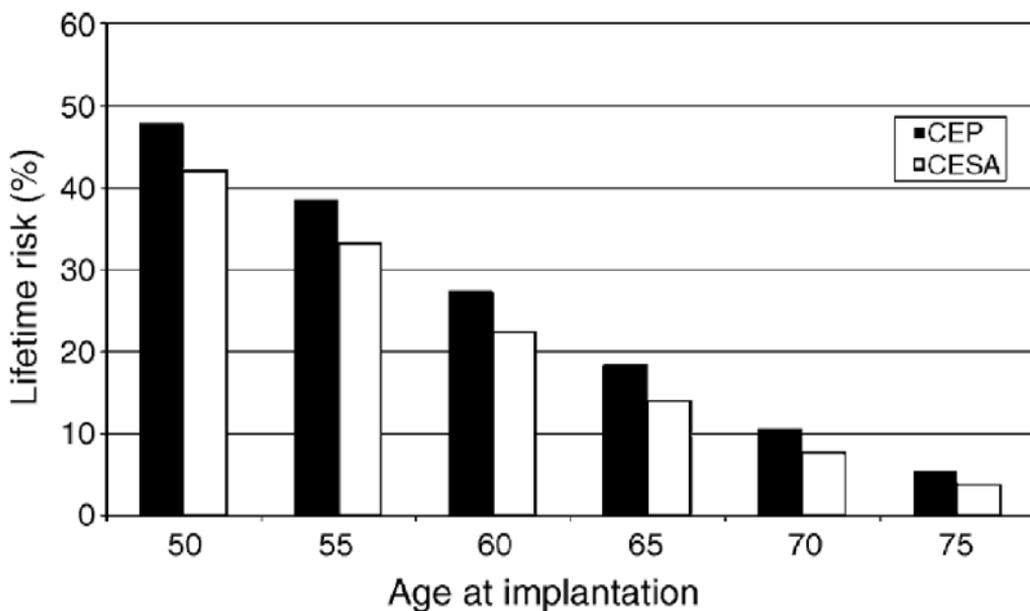


Figure 4: Lifetime risk of reoperation due to structural valve deterioration (SVD) after AVR with the Carpentier-Edwards pericardial and Carpentier-Edwards supraannular bioprostheses at different ages of implantation.

From: Puwimanasinghe JP, Takkenberg JJ, Eijkemans MJ, van Herwerden LA, Jamieson WR, Grunkemeier GL, et al. Comparison of Carpentier-Edwards pericardial and supraannular bioprostheses in aortic valve replacement. *Eur J Cardiothorac Surg*. 2006;29(3):374-9.

CE pericardial valve for aortic valve disease. A 65-year-old male, for example, has a life expectancy of 10.8 years and an event-free life expectancy of 9.1 years after AVR with the CE pericardial valve. Microsimulation models can be also be used to calculate the ‘actual’ or life time risks of valve-related events and reoperation after valve implantation. The lifetime risk of at least one valve-related event was 38% for a 65-year-old male patient and his risk of needing a reoperation due to structural valvular deterioration was 17%. Comparison of the outcome of four biological valve types (the CE pericardial and supra-annular porcine aortic valve, Medtronic Freestyle valve and allografts) using microsimulation, indicated that that there is no significant difference between these four types of biological valves in terms of survival, structural valve deterioration, or the rate of embolism and valve thrombosis<sup>10</sup>. For a 65-year-old man, for example, 10-year survival was 51% for CE pericardial valve, 51% for Carpentier supra-annular porcine aortic valve, 53% for the Freestyle valve and 56% for allografts. Life expectancy was 10.8, 10.8, 11.0 and 11.4 years, respectively, after implantation<sup>10</sup>. Another study compared the long-term outcomes of patients after AVR with the CE bovine pericardial and porcine supra-annular bioprostheses using microsimulation<sup>11</sup>. The life expectancy, reoperation-free life expectancy, and event-free life expectancy after AVR at different ages of valve implantation, for both valves, are given in Figure 3. For a 65-year-old male patient, for example, life expectancy was 10.8 and 10.9 years,; reoperation-free life expectancy was 9.9 and 10.1 years, and the event-free life expectancy 9.0 and 8.8 years, respectively, after implantation of the CE pericardial and the supraannular porcine aortic valves. In this particular study microsimulation was also used to calculate the cumulative incidence or lifetime risk of valve-related events and reoperation after valve implantation (‘actual’ analysis) (Figure 4). The results of this analysis showed that the lifetime risk of reoperation for a 65-year-old male is 18.3% and 14.0% after AVR with pericardial and supraannular porcine valves, respectively. The overall results of this study showed that both valves

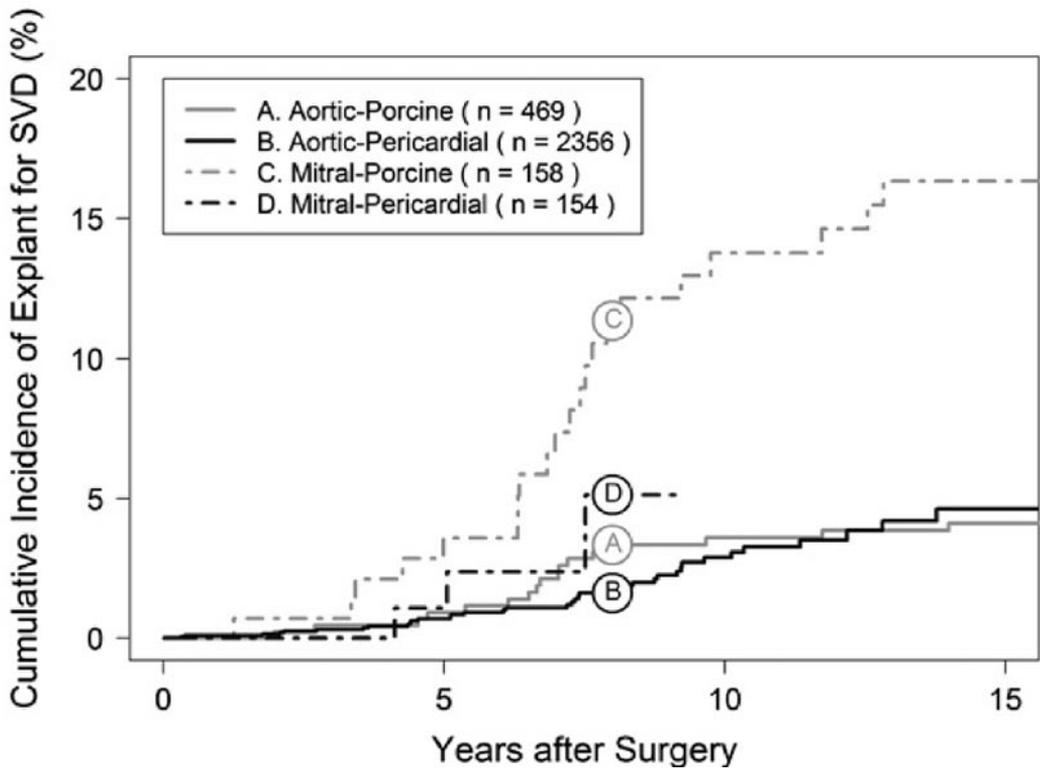


Figure 5: Cumulative incidence function estimates of explant for structural valve deterioration (SVD) in operative survivors. From: Grunkemeier GL, Furnary AP, Wu Y, Wang L, Starr A. Durability of pericardial versus porcine bioprosthetic heart valves. *J Thorac Cardiovasc Surg.* 2012;144(6):1381-6.

perform satisfactorily, especially in elderly patients, and show no appreciable difference in long-term outcomes when implanted in the aortic position<sup>11</sup>. These are examples of how microsimulation models can be very useful, for both the clinician and the patient, in the selection of optimal prosthesis in patients undergoing AVR.

The main advantages of microsimulation is that it can be used to develop new and effective evidence-based prediction tools. These models can take into account the life expectancy of the patient, the hazard of different type of events over time, allow for events to occur repeatedly and adjust the hazards of certain events depending on the events that occurred in the past. In addition, microsimulation models are also able to model two or more diseases that occur together and allocate portions of the health impact to each of these diseases. Another important advantage of these models is that they are able to simultaneously provide detailed information on, for example, the duration of the event-free period, the total number of years lived and the numbers of different types of event that individual patient experienced while standard statistical techniques can only address these issues individually. Microsimulation models have, therefore, the potential of providing the physicians an easy to use clinical decision-making tools that can be used to make evidence-based decisions. Although microsimulation models have several advantages and solve most of the methodological limitations of standard analyses methods, it still does have several limitations of its own. First, microsimulation is a simplification of reality comparable to any other currently available model used for outcome prediction. The accuracy of the model strongly depends on the extent of the available information about the patient population being studied. This means that adding more variables to the model will result in outcomes that are more comparable to reality. Since most of the input of the model is

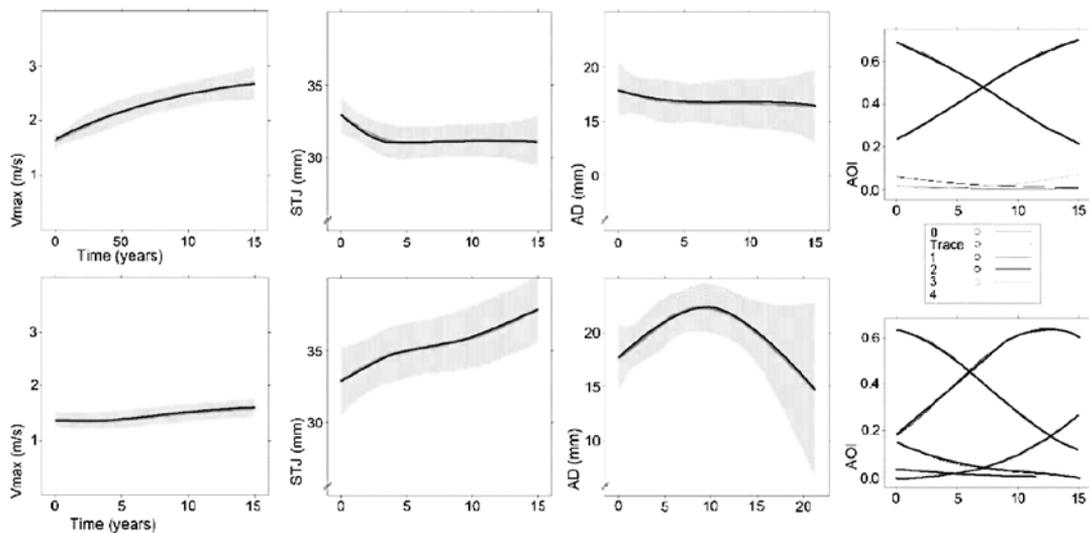


Figure 6: Peak velocity ( $V_{max}$ ), sinotubular junction diameter (STJ), annulus diameter (AD), and marginal probability of aortic regurgitation grade over time (AoI) after homograft implantation (top row) and autograft procedure (bottom row).

From: Arabkhani B, Heuvelman HJ, Bogers AJ, Mokhles MM, Roos-Hesselink JW, Takkenberg JJ. Does pregnancy influence the durability of human aortic valve substitutes? *J Am Coll Cardiol.* 2012;60(19):1991-2.

currently obtained from meta-analysis of previously published research, largely with a retrospective design, the quality of the input may be adversely affected by heterogeneity between the studies and publication bias<sup>3</sup>. In this regard, high quality data are essential for building accurate microsimulation models. Furthermore, a microsimulation model requires several assumptions regarding morbidity and mortality in the group of patients studied. For example, in case of aortic valve replacement it may be necessary to assume a constant hazard for the valve-related events other than structural valve deterioration, while hazards of certain complications (e.g. bleeding, endocarditis) will not be constant over time<sup>7</sup>. Overall, microsimulation seem to be a promising statistical tool which has the potential of important contribution to evidence-based decision making.

## Competing risks and patient outcome

Currently, actuarial methods (e.g. Kaplan-Meier, Nelson method) are the most frequently used methods in estimating the rate of an event (e.g. reoperation, bleeding) over time<sup>12</sup>. However, these methods assume that only one type of event of interest occurs during follow-up and do not take into account the existence of competing risks when estimating the rate of an event. Competing risks is defined as a patient being at risk of more than one mutually exclusive event, such as death from different causes, and that the occurrence of one of these will prevent any other event from ever happening<sup>13</sup>. As for many other diseases and treatments, taking into account competing risks can be important for the correct assessment of patient and prosthesis outcome after heart valve replacement. This is because the question answered by actuarial analysis and competing risk analysis are completely different. In case of pericardial valve implantation, actuarial methods enables us to answer the question: ‘what is the time-varying failure rate of a pericardial bioprosthesis?’. In this

example our primary objective is to investigate the properties of this particular bioprosthetic valve in isolation of the confounding “problem” that patients with this prosthetic valve may die before their valve fails. Application of competing risk analysis, on the other hand, enables us to investigate the question: ‘what is the probability that the pericardial valve fails while the patient is still alive?’<sup>14,15</sup>. The answer to this question requires that one estimates not only the intrinsic propensity of this bioprosthesis to fail, but also the likelihood that a patient will still be alive for the valve to fail. These two example show that analyzing and evaluating each event separately in a certain patient population can result in misleading conclusions. Not taking into account competing events, while they are present, will result in an overestimation of the cumulative incidences, particularly in the context of the Kaplan–Meier method.

The application of competing risks methodology is increasing in studies where cause of death is being investigated in order to obtain more realistic probabilities of death broken down by specific causes. In case there is only one type of failure and, therefore, there are no competing risk events during the follow-up of the patients the cumulative incidence estimate of the event derived using the Kaplan–Meier approach will be identical to the estimate derived from the competing risk approach. Furthermore, when researchers are only interested in the cumulative incidence estimate of the first event in the presence of multiple types of failure, application of competing risks method has also no advantages because the researchers are not interested in the subsequent events occurring after the first event. During the past decades competing risks methodology have been developed to an extent that it can relatively easily be applied in clinical research and provide useful information<sup>14-19</sup>. Using competing risks analysis, Grunkemeier and colleagues investigated the probability of pericardial and porcine bioprosthetic valves actually requiring explantation—before the patient dies<sup>20</sup>. Figure 4 shows the cumulative incidence function estimates, a method to describe events with competing risks, of explant for structural valve deterioration (SVD) in operative survivors. In this instance death was considered a competing risk, because it precludes the possibility of a future valve explant. The results of this study showed that CE pericardial valve had a subhazard ratio for structural valve deterioration (SVD) explant of less than 1 in both aortic and mitral position compared with the Carpentier porcine aortic valve. If the authors would have used Kaplan–Meier analysis in this particular study they would have estimated the rate of SVD among living patients as an isolated event. However, by using competing risks analysis they now have estimated SVD in the context of mortality before SVD occurs. This is of particular importance in older patients, where not only the biological behavior of the implanted pericardial bioprosthesis contributes to SVD, but also mortality which decreases the probability of SVD since patients will need to survive long enough to experience this event. This is from the clinical point of view an important advantage of competing risks analysis since this method allows to answer the question: “How often will elderly patients need reoperation after pericardial valve implantation, given the risk of mortality from old age itself?”



Competing risks analysis has also some disadvantages. An important assumption of time-related analysis is non-informative censoring which means that each study participants has a censoring time that is statistically independent of their pericardial or other type of valve failure time. Informative censoring occurs when study participants are lost to follow-up due to reasons related to the study. In case of competing risks analysis the probability of informative censoring increases since all events cause censoring of one another. This could lead to biased results and conclusions if the assumption of non-informative censoring is violated.

The method of competing risks can be vital in providing the clinician and the patient information about the risks they face in certain situations and can help them choose optimal treatment strategy. In addition, this method can also be used in allocation of health resources and understanding the longer term outcomes of chronic conditions. Currently, different software packages exist which can be used to perform competing risks analysis (e.g. SAS and R statistical software)<sup>21,22</sup>. Researcher should be encouraged to present both the results of the event of interest and the results of competing risks in order to be able to objectively assess the outcome of patients.

## Assessment of valve performance over time

Correct assessment of bioprosthetic heart valve function over time and the identification of potential risk factors that influence the valve function is a difficult and challenging process due to several reasons. First of all, valves are implanted in patients, who themselves have a limited survival. This creates a situation in which the risk of patient death competes with valve durability. Secondly, valve failure is a continuous process, not a hard end point. Time-to-event analysis (e.g. Kaplan-Meier, Nelson method) is therefore inappropriate when assessing echocardiographic valve function, since it considers time of follow-up as a continuous variable while echo data are usually available

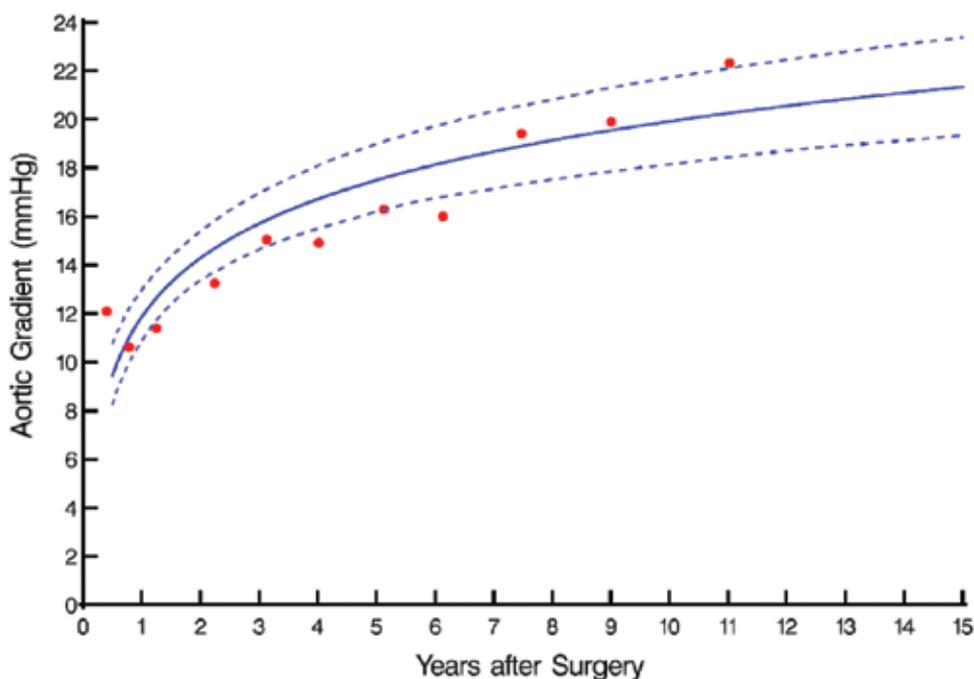


Figure 7: Aortic gradient over time in patients receiving allograft aortic valve or root replacement. Solid lines are parametric estimates of mean aortic gradient from nonlinear longitudinal mixed model and are enclosed within dashed 95% bootstrap percentile confidence bands, equivalent to 2 standard deviations. Symbols represent crude estimates of grouped raw data without regard to repeated measures and are presented to verify the model fitting.

From: Mokhles MM, Rajeswaran J, Bekkers JA, Borsboom CJ, Roos-Hesselink JW, Steyerberg EW, et al. Capturing echocardiographic allograft valve function over time after allograft aortic valve or root replacement. *J Thorac Cardiovasc Surg.* 2014.

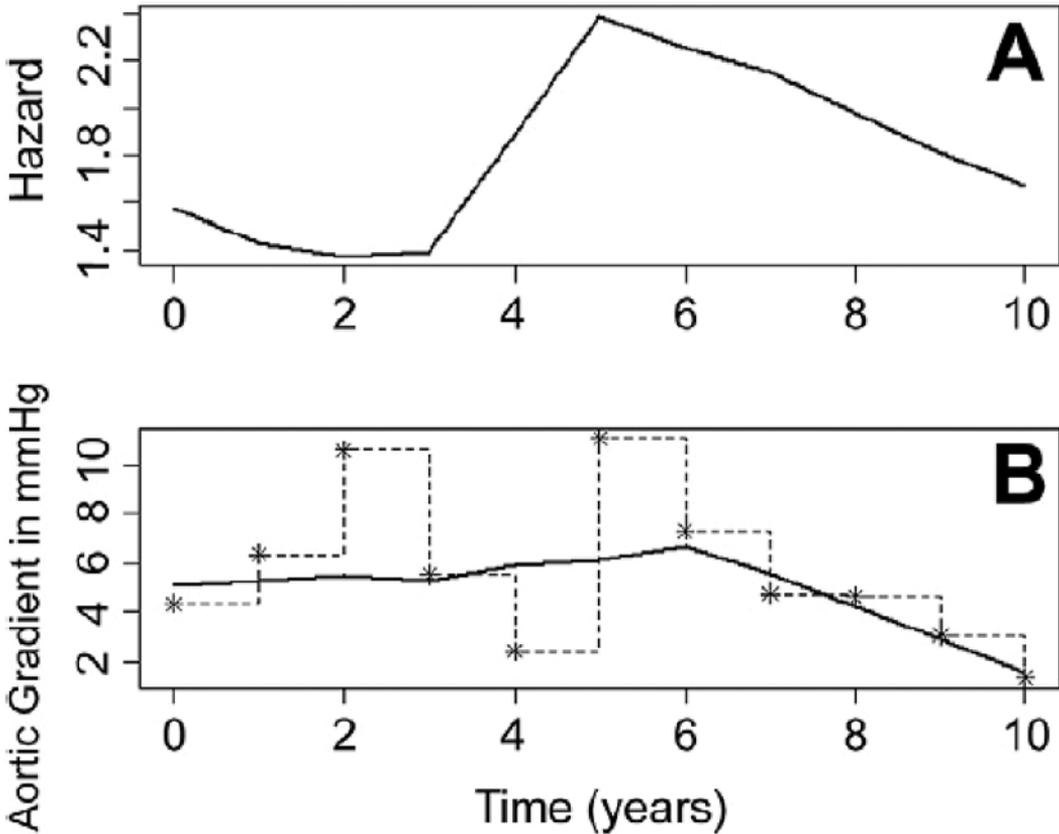


Figure 8: Graphical representation of joint models. (A) Contains the hazard function for an event. In (B), the dashed line describes a time-dependent covariate as used in the time-dependent Cox model, and the solid line the mixed-effects model reconstruction of the covariate path.

From: Andrinopoulou ER, Rizopoulos D, Jin R, Bogers AJ, Lesaffre E, Takkenberg JJ. An introduction to mixed models and joint modeling: analysis of valve function over time. *Ann Thorac Surg.* 2012;93(6):1765-72.

within a certain time frame and are often incomplete in one or more time frames. In addition, it considers valve dysfunction as an irreversible endpoint, while severity of valve dysfunction (for example aortic/mitral regurgitation) is often variable over time. Thirdly, the means by which echocardiographic follow-up is obtained may influence the results: opportunistic versus standardized follow-up, experience of the observer, and intervals between measurements may all cause bias. Finally, prosthetic valve dysfunction may present in different ways: through regurgitation, stenosis or a combination of both, further complicating valve performance analysis. The challenge in analyzing longitudinal data is, therefore, estimating the average pattern of outcome over time and its variability in the group of patients. In addition, this average must take several sampling characteristics into account (e.g. censoring by death, unequal number of observations per patient, different follow-up intervals between observations). In contrast to time-to-event methods, linear and non-linear longitudinal models are able to adequately deal with these important characteristics of longitudinal data<sup>23</sup>. Application of these longitudinal analysis methods can help the clinicians understand how a certain process changes over time and thus can contribute to a better patient management (e.g.

by determining which patients should be monitored more closely by their physicians and at which time interval).

The 2008 guidelines for reporting mortality and morbidity after cardiac valvular interventions<sup>23</sup> propose the use of longitudinal data analysis for series of assessments like repeated echocardiographic measurements of valve function to estimate its average temporal pattern and variability in a group of patients. The application of linear and non-linear longitudinal methods enables the researchers to



model the trend of various repeatedly collected data such as echocardiographic measurements over time after prosthetic valve implantation. Using these methods it is possible to visualize the temporal trend of, for example, each aortic regurgitation grade over time during follow up. Clinicians can use such temporal trends to determine on average how for example aortic regurgitation develops over time after pericardial bioprosthesis implantation.

From a statistical perspective, these types of methods are superior and more informative compared to the methods where repeated outcomes are dichotomized and analyzed with actuarial methods as if they were events, such as freedom from grade 1+ or 3+ prosthetic valve regurgitation after AVR<sup>24,25</sup>.

Several methods for longitudinal analyses exist which can be divided in linear- and non-linear methods. Both linear and non-linear structures can be used to analyze longitudinal data. An important characteristic of linear methods is proportionality since there is a straight-line relationship between the input value and the outcome. Therefore, the behavior of linear methods can, in theory, be fully predicted. However, by application of additional statistical strategies (e.g. natural cubic splines) it is possible to allow for more flexibility in the specification of the patient-specific longitudinal trajectories instead of assuming a straight-line relationship between the input value and the outcome<sup>26</sup>. Although these type of statistical methods have not yet been used to determine the function of pericardial valves, they have provided insightful information in patients receiving other type of valve prostheses. Using the method of linear longitudinal data analysis, Arabkhani and colleagues were able to show that pregnancy is not associated with changes over time in peak velocity, sinotubular junction diameter, annulus diameter, and marginal probability of aortic regurgitation grade, in patients receiving a homograft or autograft for aortic valve disease (Figure 6)<sup>27</sup>. These results indicate that the durability of human tissue valves is not affected by pregnancy, making these valves a good choice for aortic valve replacement in young patients with severe aortic valve disease who are planning to become pregnant.

In non-linear methods, the model uses parameters that are allowed to vary. Therefore, the assumption of proportionality is absent in non-linear models and the behavior of such a model cannot be fully predicted. The cardiovascular system is a complex mechanical, chemical, and hemodynamic system in which the processes are often related via a variety of mechanisms. Therefore, these processes are often non-linearly structured<sup>14,28-31</sup>. Since the principle of proportionality may not be valid, using linear methods may result in simplification of the real process and therefore inaccurate results and inferences. For example, the application of these methods showed that, in patients undergoing allograft aortic valve or aortic root replacement, the increase in transaortic gradient is non-linearly shaped over time (Figure 7). The aortic gradient in these patients increases mainly in the first 5 years after heart valve replacement<sup>14</sup>. The researchers would not be able to visualize this trend if linear methods would have been used to analyze the data of these patients. On the other hand, the application of non-linear models is relatively time-consuming and more advanced. Thorough

statistical knowledge on longitudinal analyses methods is required to perform these type of analyses. However, if the clinicians are aware of the existence of these methods and can recognize when it should be applied they can consult a biostatistician who can help them analyze their data.

Both the linear and non-linear methods are more advanced and time consuming compared to the application of, for example, actuarial methods for the analyses of serial data. However, these methods are more reliable and reproducible, and can be done using standard available software (e.g. SAS and R statistical software). Researcher should be encouraged to collect every observation of longitudinal outcome (e.g. NYHA classification, cardiac rhythm, valve function, etc) and analyze the data using longitudinal methods in order to obtain reliable outcome estimates and conclusions.

## Joint-modeling

Several well established classical models exist for the separate analyses of longitudinal data (e.g. aortic gradient and regurgitation, ejection fraction) and time-to-event data (e.g. reoperation, endocarditis, death). However, these classical models do not consider dependencies between these two different data types which can lead to inefficient or biased results when the longitudinal data is correlated with time-to-event data. Over the last two decades an increased attention has been given to combining longitudinal data with time-to-event data. This approach is called joint-modeling and enables the researchers and clinicians to investigate, for example, in which degree serial echocardiographic measurements, certain biomarkers or ECG values are capable of predicting events (e.g. death or reoperation) that patients might experience after a treatment (e.g. pericardial bioprosthesis implantation)<sup>32-34,35,36</sup>. The overall objective of joint-modeling is to characterize the relationship between a longitudinal response process and a time-to-event in longitudinal studies. This approach can particularly be useful in the field of heart valve surgery since valve function is periodically monitored over time after surgery. Using this approach will allow the researchers to not only take into account the initial or current valve function, but also the rate at which the valve function deteriorates over time in order to determine the future prognosis of the patients (e.g. reoperation or death hazard)<sup>32</sup>.

In joint-modeling, typically a mixed-effects model is used for the longitudinal data and a Cox model for the survival data in order to build a single model where dependency and association between these types of data is taken into account (Figure 8)<sup>37,38</sup>. An important advantage of mixed-effects model in analyzing longitudinal data is their ability to correctly handle with the datasets that contain unequal number of follow-up measurements between subjects and varying times between repeated measurements of each subject. Furthermore, these models are able to take into account that measurements from the same patient may be more correlated than measurements from different patients. This approach can ultimately lead to a less biased and more efficient identification of potential prognostic factors of a certain outcome<sup>37</sup>. The problem with the application of joint modeling is currently the complexity of the analyses and lack of appropriate software. Although, there were tremendous developments within the field of joint modeling over the past decades, the availability of software to implement these methods lags behind. It can be expected, however, that this issues will become less important when freely available and easy applicable software will become more readily available. Currently, software for performing joint-modeling analyses is available in statistical software packages as R statistical package and SAS (SAS Institute, Cary, NC)<sup>39</sup>.

## Conclusions

Although several innovative statistical methods have been developed and are currently available for the analysis of outcome in cardiac surgery, only a few of these methods are widely used. The methods that are currently used for determining the patient outcome have often important limitations and are not suitable to the analysis of the available data. It can be expected that with application of novel statistical methods researchers and clinicians will obtain more reliable estimates of different types of events in patients receiving pericardial valves leading to more reproducible results and conclusions. Investigators should, therefore, be encouraged to apply these novel methods more often when assessing patient outcome and valve performance over time following pericardial valve implantation.



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Chapter 6

# The Future of the Pericardial Valve

*Thomas A. Barker and Gebrine El Khoury*

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*It is good to be sceptical but foolish to believe in nothing*

Arnold M. Seligman (American Surgeon)

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## Introduction

Since the ground-breaking characterisation of rheumatic fever<sup>1</sup>, the need for cardiac surgical correction of valvular lesions increased considerably. Although in certain areas of the world this disease is still prevalent, Western societies have witnessed a marked reduction in the incidence of rheumatic fever<sup>2</sup>. Consequently, this has resulted in a change in valve pathology from rheumatic to a predominantly degenerative aetiology. Whatever the cause of a particular valve lesion may be, generally there is a vast surgical experience for dealing with these highly debilitating and often fatal conditions.

To date, since their invention and clinical use, valve prostheses have provided the mainstay of surgical interventions for heart valve disease. The evolution of valve prostheses technology, encompassing mechanical and biological valve substitutes has been a complex area of debate within the cardiac surgical world.

Furthermore, over the past thirty years, the increasing use of reparative techniques, initially for the mitral and more recently for the aortic valve, has added to the complexity of decision making for the cardiac surgeon. Regurgitant lesions are often amenable to such repairs although it is now known that certain stenotic valvular lesions can also be corrected. Moreover, stentless valves, autografts and homografts further complicate the picture as these valves have potential advantages for treating, amongst other pathological processes, endocarditis-damaged valves and their annuli.

The purpose of this chapter is to describe and critically evaluate the future of the pericardial valve prosthesis. We consider if the mechanical or the porcine bioprosthesis could compete with the technology on which the pericardial valves are built. In addition, by playing 'Devil's Advocate' we take the approach of presenting the evidence for the alternatives to the pericardial valves. We hope to identify whether, in years to come, the pericardial valve will be overshadowed by other technologies or whether it will, after all, be established as the 'Gold Standard' for heart valve replacement.

The hallmarks, the protagonists, and the timing of the introduction in clinical use of the various heart valves and the technologies on which they were built are well described in the first chapter of this book.

## Perspectives On Competition From Current Stented Prostheses

### Is mechanical or biological the future?

The ideal heart valve should possess good haemodynamic performance, no risk of structural deterioration - therefore excellent durability, should be non-thrombogenic, should carry a low risk of endocarditis and should be easy to implant<sup>3</sup>. Essentially, they should mimic the non-diseased native valve. In reality, such a valve does not exist, so when diseased heart valves are replaced, there is a transfer of sequelae from the inherent native valve pathology, to the sequelae of the prosthetic valve. The latter, although often being a better choice of the two options, it carries in itself certain risks to the recipient. The vast majority of severe symptomatic valvular heart disease is treated surgically by stented prostheses which are broadly divided into two groups, mechanical or biological.



Mechanical prostheses, in the shape of ball and cage devices were first used in 1961 to replace mitral valves<sup>4</sup>. The initial safety of these prostheses was demonstrated by the publication of the results of 100 aortic valve replacements without operative mortality<sup>5</sup>.

Modern mechanical valves are made of pyrolytic carbon combined with metallic or polymeric components.

The first stented bioprostheses were the porcine aortic valves, manufactured and distributed first by Hancock Inc., followed shortly thereafter by other porcine valves manufactured by different laboratories (Edwards, Mitral Medical, Shiley).

The second type of bioprostheses is the pericardial xenograft created in England in 1971 and manufactured by Shiley Inc in California.

A variety of chemical interventions were proposed and tried on the bioprostheses with the aim to prevent or mitigate tissue calcification<sup>6</sup>. There has not been any clinical evidence whatsoever of the efficacy of such treatments.

The choice for the most appropriate type of bioprosthesis depends on a number of factors including patient's age, the presence of co-morbidities, life expectancy, indications and contra-indications for warfarin treatment, socio-economic situation and last, but not least, patient preference.

There were two important pivotal studies that compared mechanical prostheses to bioprostheses for both aortic and mitral positions. The first was the Edinburgh Heart Trial which showed that survival at 20 years was not different between the two, although mechanical valves had lower reoperation rates. There were no differences in the rates of occurrence of endocarditis or of thrombosis and embolism<sup>7</sup>. The other study was the Veteran's Affairs (VA) Trial which actually



showed that in the aortic position there was a survival advantage at 15 years for patients receiving a mechanical prosthesis. This was not the case for the mitral position. However, the better survival found with the mechanical aortic prostheses was not evident in patients over the age of 65 years; The reoperation rates increased with decreasing age for bioprostheses<sup>8</sup>. Therefore, ten years ago

these two studies established a consensus to recommend the use of mechanical prostheses in patients less than 65 years, and bioprostheses over this limit.

One of the major drawbacks of mechanical valves, highlighted by these studies, was the risk of bleeding caused by the use of anticoagulation to avoid valve thrombosis. Warfarin, per se, in patients with heart disease is responsible for a bleeding complication rate of 2.3–6.8% per patient year<sup>9</sup>. In patients with mechanical prostheses in either position, the bleeding rate is 0.3–1.7% per patient year<sup>8,10–11</sup> compared with 0.33% per patient year for bioprostheses. Bleeding rates have been shown to be lower in younger patients<sup>12</sup> and the large variability of INRs is a risk factor for worse survival<sup>13</sup>, and its better control can improve survival<sup>14</sup>. With anticoagulation however, valve thrombosis rates are very low at 0.1% per patient year. Thromboembolism risk is also no different between mechanical and biological, 0.3% and 0.34% per patient year respectively<sup>11,12</sup>. This conclusion was also made in the Edinburgh and VA Trial, although the percentage of patients treated with anticoagulants was not stated.

An important consideration, in valve choice, is the potential for a reoperative procedure. For mechanical prostheses, valve thrombosis rates are low at 0.1% per patient year<sup>12</sup>. For biological valves, structural valve deterioration (Figure 1) occurs at a similar rate of 0.16% per patient year<sup>11</sup>. For redo aortic valve replacement, lower mortality rates are described if the initial placement was a biological prosthesis<sup>15–16</sup>. This is due to the mode of deterioration with mechanical valves presenting more acutely as an emergency due to thrombosis or endocarditis, compared with a more chronic, progressive deterioration for biological valves that undergo structural valve failure<sup>17–19</sup>. The ability to manage bioprosthesis deterioration more conservatively also makes the likelihood of the reoperative procedure being undertaken electively<sup>20</sup>. Not all reports agree, however, that there is a difference

in reoperative outcomes with mechanical or biological valves<sup>21</sup>. Re-operating on patients with prosthetic valves, if they develop structural valve deterioration, is not without risk. The hospital mortality ranges from 4.8–7.8% for aortic valve redos<sup>16,22–26</sup>, 6.8–7.4% for mitral redos<sup>16,25–27</sup>, 11.5–14.3% for double valve redos<sup>16,25</sup>, and tricuspid redos 25.6%<sup>16</sup>. An alternative to reoperation is the 'valve-in-valve' procedure (TAVI) which may become prevalent in years to come, with equivalent mortality rates of 6.4% in some series<sup>28</sup>.

Although historically 65 years of age has been the appropriate 'cut-off' for whether a mechanical or biological valve was advised by surgeons<sup>29–30</sup>, increasing evidence suggests that bioprostheses may be the better option below this age. When advising on prosthesis type, the patient's life expectancy is clearly an important consideration, as factors such as cardiovascular comorbidities can reduce this<sup>31</sup>, and thus reduce the likelihood of a reoperation if a biological valve was implanted. Some studies have shown that above 60 years old, there is no difference in valve related reoperation rates for aortic prostheses<sup>32</sup>. Microsimulation computer modelling shows that for a 60 year old, life expectancy is no different with a biological or mechanical prosthesis (11.9 vs 12.2 years). Reoperation rates were higher for biological, but bleeding risk higher for mechanical, 12% vs 14%<sup>33</sup>. Over 70 years old, the risk of a major bleed is 24% compared to a reoperation rate of 12% at 12 years<sup>34</sup>. Bleeding complications increases with age and target INR<sup>35</sup>, and this, along with the evidence above, contributes to the consensus now for surgeons to advise bioprostheses to patients over 60 years old for aortic valve and 65–70 years for mitral replacements<sup>36</sup>. When operative mortality and operative redo mortality, along with risk of valve related mortality and morbidity are added up for a 50 year old man undergoing aortic valve replacement, bioprostheses have cumulatively less risk over a 30 year period<sup>37</sup>. Hence, there is a general consensus of surgeons to use bioprostheses in younger patients<sup>38</sup> which makes the future for pericardial valves extremely promising.



*Figure 1: An explanted porcine valve showing calcific degeneration.*

## Should we choose porcine or pericardial?

In the current trend of using bioprostheses in increasingly younger patients continues, the next question regarding the future of stented pericardial valves is, 'What impact will alternative stented bioprostheses have on the market share?' The main alternative are the porcine bioprostheses and the two large randomised trials comparing the performance of mechanical and bioprostheses included porcine aortic and mitral prostheses<sup>40</sup>. Therefore, although these trials used outdated technology, long term results of randomised series for porcine valves are available. The clear disadvantage of a bioprosthesis, is the increased need for reoperation due to the potential for structural valve deterioration;. At 20 years, the mode of deterioration of porcine valves was three-quarters regurgitation and a quarter stenosis<sup>39</sup>. Some reports have found that porcine valves have a higher rate of deterioration, and thus a lower freedom from reoperation, than pericardial valves<sup>40</sup>. This degeneration is lower in older age groups of patients due to the less severe haemodynamic stress the

valve is exposed to, but mainly due to calcification<sup>8,41-42</sup>. Porcine prostheses primarily degenerate by leaflet tears rather than by calcification often associated with pericardial prostheses<sup>19,42-45</sup>. Some have, therefore, suggested that this difference makes clinical presentation more acute for porcine valves and potentially results in worse outcomes from more urgent redo surgery<sup>19</sup>.

Another important consideration when choosing between porcine and bovine valves is the haemodynamic performance of the prostheses. Indeed, effective orifice areas are considered to be predictive of survival following valve replacement. If these are inappropriately small, this is called patient-prosthesis mismatch<sup>45-49</sup> and the patient is left with post-operative transvalvular gradients which will impact on left ventricular remodelling. Ultimately, it is left ventricular mass that predicts a patient's cardiovascular future<sup>50</sup> and left ventricular mass regression is a predictor of survival after aortic valve replacement<sup>51</sup>. Pericardial valves have lower transvalvular gradients<sup>52</sup>, larger effective orifice areas<sup>53</sup> and, consequently, lower incidence of patient-prosthesis mismatch. In particular, pericardial valves have excellent effective orifice area (EOA) even in small valve sizes<sup>54</sup>. Although better haemodynamic performance has not been shown to impact on early LV remodelling<sup>53,55,56</sup>, it has been shown to produce LV mass regression at 5 years post-operative<sup>57</sup>. There are reports, however, which find no difference between transvalvular gradients and EOA between two different types of porcine bioprostheses of second and third generation<sup>58</sup>. Many institutions have moved over to using primarily pericardial valves, due to their haemodynamic superiority and durability<sup>59</sup>. The future, in terms of bioprosthesis choice, we feel, favours pericardial valves and that this will become more apparent in the coming decades.

## What Are The Alternatives To Stented Prostheses?

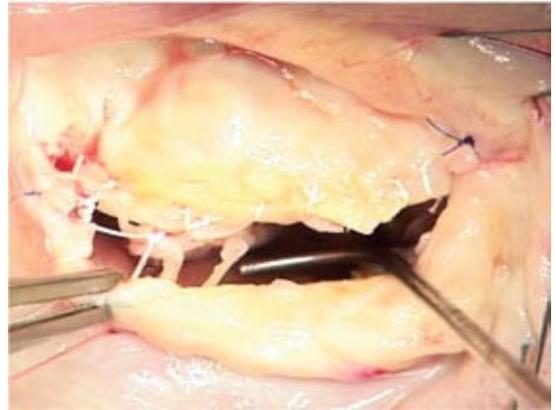
### Mitral valve repair

Mitral valve repair, which was first created and introduced into clinical use by Geoffrey H. Wooller in 1957 as 'Mitral Annuloplasty', has since been modified, refined and popularised by several other surgeons<sup>60</sup>. This procedure is now an established approach for treating a variety of mitral pathologies. Since then, alternative repair techniques have been undertaken and shown to have durable results with excellent mid to long-term freedom from reoperation<sup>61-62</sup>. Most types of valve dysfunction can be addressed and the treatment of posterior, anterior and bileaflet prolapses can be successfully corrected<sup>63</sup>. The effects on left ventricular function following the destruction of subvalvular structures when the valve is replaced, has led to the general belief that valve repair is superior to replacement<sup>64-65</sup>. Particularly in high volume centres, most degenerative mitral regurgitation should be expected to be treated with a repair. Series have reported showing survival for non-rheumatic mitral repair to be 48% at 20 years, similar to the age matched general population<sup>66</sup> as well as and 96.1% freedom from reoperation<sup>67</sup>. These reparative techniques allow the potential for patients to avoid long-term anticoagulation and also avoid the risk of structural valve degeneration. Developments in this area has reduced the need for stented mitral valve prostheses.

Another pathology amenable to repair techniques is rheumatic mitral disease (Figure 2), with post-repair survival at 20 years of 82%. The drawback of repairing rheumatic mitral valves is the need for repeat surgery in the future, as freedom from reoperation is only 55% at 20 years. Despite the risk of reoperation and the technically demanding nature of the surgery, low rates of thromboembolism in addition to the advantages already described, make repair the preferred option in this setting<sup>68,69</sup>.

In addition to degenerative and rheumatic disease, the treatment of endocarditis has excellent results with valve repair, with recurrence of infection as low as 1.6%<sup>70</sup>. Surgeons with experience in these areas will use very few stented valve replacements, in most instances.

The management of ischaemic mitral regurgitation is one area which lacks clarity in deciding whether to repair or replace. For acute ischaemic papillary muscle ruptures, replacement is thought to be the safest approach<sup>71</sup>. However, for chronic ischaemic mitral regurgitation, there remains controversy as to which option is best. A large propensity-matched study showed survival to be superior if repair was undertaken<sup>72</sup>. In addition, improved short-term and long-term survival with repair was observed in a meta-analysis<sup>73</sup> despite one previously showing only improved short-term, not long-term, survival<sup>65</sup>. However, this is one area of mitral surgery that has recently been tested with a randomised trial which showed that there was no difference in survival or clinical outcomes whether the valve was repaired or replaced. The interesting, and probably expected finding, was that moderate-severe post-operative regurgitation was higher in the repair group<sup>74</sup>. Therefore, replacement seems to be a reasonable option in this group of patients<sup>75</sup>, although many surgeons still feel that each situation should be judged on its merits, as often it can be successfully corrected by repair. Therefore, the pericardial bioprosthesis may still have a role to play in the future of mitral valve disease after all.



*Figure 2: A complex mitral repair for rheumatic disease: leaflet patching with pericardium in conjunction with gortex cords.*

## Aortic Valve repair

The major advantages of this approach, as with mitral repair, is the prospect of the patient not requiring anticoagulation<sup>76-78</sup>, lower levels of thromboembolism and lower levels of endocarditis<sup>79</sup>. In addition, structural valve degeneration associated with stented prostheses can be avoided. Another advantage is that the aortic root changes, often associated with leaflet pathology, can be addressed during a repair operation<sup>80</sup> with no significant worsening of outcome<sup>81</sup>. There are generally two common ways to stabilise the aortic root as part of repair procedures – remodelling (Yacoub), or valve sparing reimplantation technique (David). Some reports suggest excellent outcomes with either procedure<sup>82-83</sup>, some with remodelling<sup>84</sup> and some with the reimplantation technique<sup>85</sup>. At present, it is clearly an area of cardiac surgery that is rapidly developing.

Historically, significant numbers of valve repair have been undertaken in a few, high volume centres around the world. It has been shown that high levels of experience with these techniques, as expected, does improve outcomes<sup>86</sup>. Such centres have reported perioperative mortality rates of 0.6%, overall survival at 8 years of 88%<sup>87</sup>, other show 10 year survivals at 82-88%<sup>78-85</sup>. No incidence of thromboembolism or endocarditis have also been reported and is a clear benefit of the repair approach<sup>78</sup>. Repair techniques have also been utilised for aortic valve endocarditis<sup>88</sup> and freedom from reoperation at 10 years can be 85%-89%<sup>78,85</sup>.

It is now accepted, that in experienced hands, bicuspid as well as tricuspid valves can be successfully repaired (Figure 3)<sup>89-90</sup> although outcomes are slightly worse in terms of reoperation rates<sup>91</sup>. The

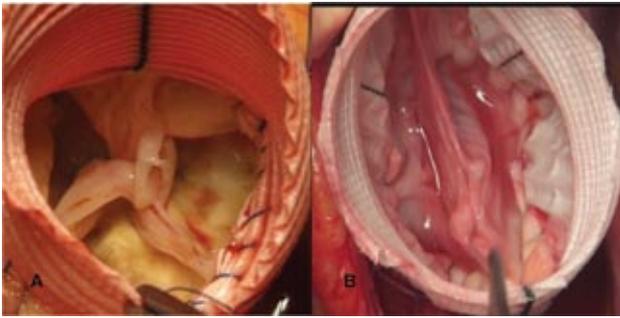


Figure 3: Re-implantation 'David' aortic valve repair:  
A) Tricuspid repair B) Bicuspid repair.

success of aortic valve repair techniques are, however, affected by the nature of the aortic regurgitation. Restrictive leaflet disease has reoperation rates of about 16% at 5 years compared to 7% and 5% for normal or excessive leaflet motion valve dysfunction<sup>92</sup>. This is partly due to the difficulty in achieving good post-repair leaflet coaptation, which is vital for durability<sup>93</sup>. For this reason, aortic valve repair has lagged behind mitral repair<sup>94</sup> as only approximately 2% of aortic valve pathology is amenable to repair due to the vast majority of disease being calcific aortic stenosis<sup>95</sup>. Despite major strides being made in this field, the small number of specialist centres treating the relatively few suitable patients means that, globally, aortic valve repair does not pose a significant challenge to the pericardial aortic bioprosthesis in the foreseeable future.

### Aortic homografts

There is extensive experience of the use of aortic homografts, particularly in the setting of treating endocarditis, as well as other indications including aortic dissection and aneurysms. They are technically challenging to implant, but operative mortalities can be as low as 2.9%<sup>96</sup>. The subcoronary approach has a higher rate of post-operative aortic regurgitation compared with the full root replacement with coronary implantation, the technique favoured by most surgeons<sup>97-98</sup>. A benefit of this complex implantation is the advantage of excellent haemodynamics, resulting in more left ventricular mass regression being observed when compared to stentless or stented aortic prostheses<sup>99</sup>. As with other stentless valve choices, questions over durability have been raised although overall freedom from reoperation in some series is satisfactory at 87.9% and 49.5% at 10 and 20 years<sup>96</sup>. Younger patients receiving homografts, however, do tend to have higher rates of structural valve degeneration<sup>98</sup> which results in regurgitation<sup>96</sup>. In addition, when compared to porcine bioprostheses, aortic homografts have worse long-term durability<sup>100</sup> which is a significant concern given the hazardous nature of the redo surgery, often requiring extensive decalcification<sup>101</sup>.

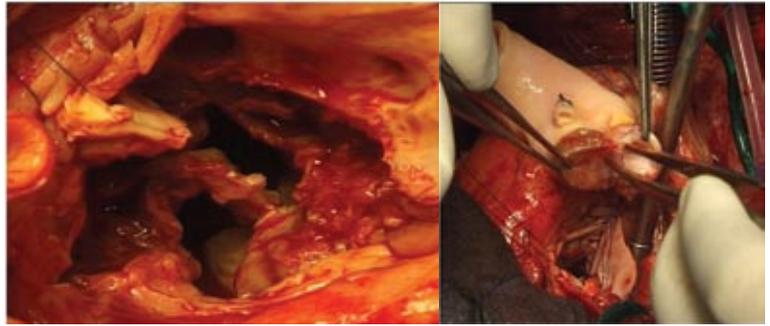
The primary use of aortic homografts is to treat endocarditis, as they can conform to the native tissue defects left following extensive debridement of infected tissue, often required in complicated native or prosthetic valve infections (Figure 4)<sup>102</sup>. When the aorta has to be disconnected from the left ventricle, the ability to reconstruct the aorto-mitral continuity is a significant advantage of homografts, avoiding the need for time consuming pericardial patching. Prosthetic valve endocarditis is a difficult condition to eradicate, but if managed with a homograft, recurrence rates range from 0 to 20%<sup>103-107</sup> which are lower than if a prosthetic valve replacement is used<sup>108</sup>. However, realistically, limited access to homografts, the challenging nature of the surgery, along with a small amount of appropriate patients do not make homografts a significant challenge to the future of pericardial valves.

Nonetheless, homografts will remain a valuable part of the surgeon's armamentarium, particularly for managing complex endocarditis.

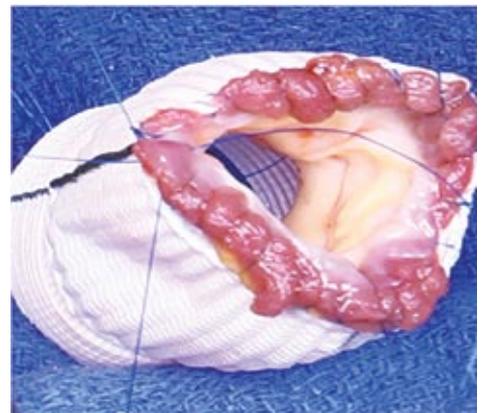
### The Ross procedure

Donald Ross reported the use of autografts to treat valvular heart disease for the first time in 1967<sup>109</sup>. The major advantage of the Ross procedure is the potential for valvular growth in younger patients who require aortic valve replacements. The additional advantage of the avoidance of anticoagulation<sup>110</sup> makes this an attractive concept. However, some have raised concerns in advocating its use, particularly due to a fear of late failures<sup>111</sup> and higher mortality rates, double that of stented valves<sup>112</sup>. Reports of a 55% pulmonary autograft dilatation rate at 7 years were of clear concern, even though this dilatation was not always accompanied by significant aortic regurgitation<sup>113-114</sup>. A systematic review showed that results are actually good but after 10 years, autograft problems become more prevalent<sup>115</sup>. Technically, this operation is extremely challenging and even though there are reports of freedom from reoperation of rates of 91% at 10 years<sup>116</sup>, modifications over the years have seen a move away from the subcoronary approach, towards a full root replacement due to initial problems with aortic insufficiency. In addition, to address the issue of autograft dilatation, modifications have included some performing aortic annulus remodelling<sup>117</sup>, the root inclusion, the use of a Dacron support graft for the autograft or a Valsalva support graft (Figure 5)<sup>118-121</sup>. The long-term outcomes of these are awaited.

Despite criticisms in the past, many groups around the world have persevered and started to publish the mid-term to long-term results of their experiences. Although, the literature will only portray a positive skew to the results of the Ross procedure due to publication bias, it is clear that in experienced hands, the results of this procedure are as good, if not better than the alternatives available. Operative mortality ranges from 0-5-5.2%<sup>110,116,122-127</sup> and late mortality has been reported as high as 97% at 16 years<sup>117</sup> and 93.6% at 20 years<sup>128</sup>. Freedom from autograft reoperation can be as good as 81.8% and freedom from homograft reoperation 92.7% at 20 years<sup>128</sup>. Thromboembolism occurs at a rate of about 0.25% at 16 years<sup>125</sup> even in the absence of anticoagulation<sup>110</sup>. Finally, endocarditis occurs at a rate of 3.5% at 6 years<sup>116</sup> and 5% at 16 year<sup>125</sup>. The Ross procedure is also a useful approach



*Figure 4: Treatment of a complex aortic prosthetic valve endocarditis A) Extensive debridement of the aortic root and aorto-mitral continuity B) Aortic homograft used to reconstruct the ventricular-aortic junction.*



*Figure 5: A modification of the Ross procedure; the pulmonary autograft is mounted in a Valsalva graft to prevent autograft dilatation in the future.*

for treating aortic valve endocarditis with low mortality (3.8%) and low reinfection rates<sup>123</sup>.

Despite impressive results from a small number of high volume specialist centres, for the vast majority of surgeons who are inexperienced in performing the Ross procedure, it is not a viable alternative to the pericardial bioprosthesis. Although the haemodynamics of autografts rival those of non-diseased aortic valves, new generation pericardial bioprostheses are not far behind<sup>129</sup>. Therefore, the Ross procedure will not prove to be a significant contender to the future of the pericardial valve.

### Stentless bioprostheses

Stentless prostheses have received mixed reviews over the last two decades with questions over durability. The 'Toronto Stentless Valve' has provided good survival, but has shown suboptimal rates of structural valve degeneration, approaching 50% for patients less than 65 years old at 12 years follow-up<sup>130</sup>. Even though other analyses have found lower rates of freedom from reoperation for stentless valves compared to stented porcine valves<sup>131</sup>, other reports have been more encouraging. Excellent durability data has been reported for the Freestyle stentless valve, with 10 year freedom from degeneration of well over 90% (Figure 6)<sup>132</sup>. The issue of durability is even more important for stentless technology as reoperations following stentless valve failures are extremely challenging procedures and carry significant mortality rates<sup>133</sup>.

There has been an evolution in the technology of stentless prostheses starting with 1st generation (Freestyle, Prima, Toronto, O'Brien, Biocor), 2nd generation (Shelhigh), and now 3rd generation pericardial stentless prostheses (Pericarbon Freedom, Equine 3F). The insertion of these valves is more technically demanding than stented valves and results in longer operative time, bypass and



*Figure 6: Implantation of a Freestyle stentless aortic prosthesis*

ischaemic times. Developments in the design have aimed to make them more user friendly in order for implantation to be easier. The absence of a sewing ring results in improved, effective orifice areas and transvalvular gradients superior to stented aortic prostheses<sup>134-136</sup>, making them particularly useful in elderly patients with small aortic roots. These better haemodynamics result in early improvements in LV mass regression<sup>137</sup>, however, the remodelling seen in stented prostheses is delayed, so differences are not observed beyond a year<sup>138-139</sup>. It has also been suggested that stentless valves have particular advantages in patients with poor left ventricular function as they produce greater improvements in ejection fraction post-operatively<sup>140</sup>. In

addition, freedom from valve related morbidity is another potential advantage of these valves, with extremely low five year thromboembolism rates of 3% and endocarditis of 1%<sup>141</sup>; these comparing favourably with stented prostheses. Stentless valves also have benefits in treating endocarditis with low reinfection rates observed<sup>142</sup>.

Although some have shown superior midterm survival for stentless valves when compared to stented prostheses<sup>143</sup>, controversy still exists, as this is not a universal finding<sup>144</sup>. From the experience at our institution, we strongly believe that stentless valves have a significant future in treating aortic

valve disease with very few patients returning for redo surgery. The ability to address root pathology or unfavourable root dimensions at the same time as replacing the valve makes them extremely versatile prostheses. The future of the pericardial valve is therefore likely to be enhanced through the new generation of pericardial stentless prostheses, however, the long-term results will define how these valves will be utilised in future decades. Even if these results were unexpectedly poor, the future of the pericardial valve still remains strong as certain new generation stented pericardial valves have also been shown to have haemodynamic profiles that can compete with stentless technology<sup>145</sup>.

### **Polymeric heart valves**

Polymeric heart valves are constructed from polymeric materials that can be specifically designed for optimum performance. The advantage of a fully synthetic valve would be the ability of valve manufacturers to specifically design its components to have certain specific molecular composition that resulted in low gradients in combination with little or no structural valve degeneration and low thrombotic risk. Unfortunately, when they were initially tested some time ago<sup>146-147</sup>, these valves gained a poor reputation for exactly the opposite characteristics. The sub-optimal haemodynamics<sup>148</sup> and the high propensity to calcify<sup>149</sup> resulted in the preferred use of the mechanical and biological valves we see in use today. Over the last decade, ongoing development in this area has continued with new polymers being designed and tested. Such polymers include a variety of biologically stable polycarbonate urethanes<sup>150-151</sup> and nanocomposite polymers<sup>152</sup>.

A new polymer with potential is a polyolefin thermoset elastomer (xSIBS) which may prove to be a material that doesn't degenerate over time<sup>153</sup>. Evidence to suggest that polymeric valves are resistant to calcification is now starting to emerge<sup>154</sup> although much further confirmation is awaited. With percutaneous polymeric valves being developed<sup>155</sup> it will be interesting to see if the chemists can revolutionise valve replacement. The introduction of polymeric heart valves is not going to be straight forward, however. Extensive pre-clinical animal testing will be necessary, prior to human trials. Safety testing will have to be extensive and include material property testing, biological safety, haemodynamic performance, durability, fatigue and corrosion testing. In addition, magnetic resonance compatibility and shelf life assessments will have to be made<sup>156</sup>. Future decades will show if this technology can be adopted. It is reasonable to conclude that polymeric heart valves do not provide an immediate threat to the use of current use of pericardial valve prostheses.

### **Tissue engineered valves**

Developments in tissue engineering in many aspects of medicine is an extremely exciting prospect, providing the promise of novel methods of addressing surgical conditions. By producing heart valves using this technology, surgeons could potentially have the ability to insert personalised valves into patients, populated by cells that originate from the recipient's own body. It is hoped that such valves would have the potential to grow and remodel, which would be a major advantage in younger patients. In addition, this could result in prostheses which do not suffer from the inherent problems of structural degeneration found with biological prostheses currently available, including pericardial valves. The hope is that a valve engineered from living cells is more biologically compatible with its environment and thus, has the potential to self-repair if degeneration starts to occur. In particular, self-repair potential would overcome the problem of mechanical damage induced by percutaneous delivery of such prostheses<sup>157-159</sup>.

Two approaches to achieve tissue engineered heart valves have been investigated, the first being ‘In situ tissue engineering’, which involves implanting a scaffold, whose molecular design attracts cells to migrate to it and become integrated within it, in order to produce the valve prosthesis<sup>160</sup>. An example of this is a Nitinol stent being inserted into the abdomen of a beagle which promoted



ingrowth of tissue<sup>161</sup>. The second option is ‘In vitro tissue engineering’ which provides a manufactured scaffold which is seeded with cells harvested from the recipient. This is then cultured in vitro to form the final prosthesis prior to implantation<sup>162</sup>. A variety of scaffolds are under investigation including polymerised extracellular matrices<sup>163-165</sup>, degradable synthetic scaffolds<sup>166</sup>, decellularised xenograft valve scaffolds<sup>167</sup> and Nitinol, nickel titanium based scaffolds<sup>161</sup>.

Seeding scaffolds has been the focus of many groups around the world. In particular stem cell seeding has been a popular target as the pluripotent nature of such cells have the potential to differentiate into all cell types required to produce a durable tissue engineered heart valve. A host of pluripotent cells have been tested, including bone marrow derived cells which have had promising results<sup>166,168-170</sup>. Although bone marrow derived cells would be a very accessible cell source, some reports have found that retention within scaffolds is limited<sup>171</sup>. Other cell types tested have included adipose derived mesenchymal stem cells<sup>172</sup>, circulating endothelial progenitor cells<sup>169</sup>, umbilical cord derived cells<sup>173-175</sup>, chorionic villus-derived stem cells<sup>176</sup> and amniotic fluid derived progenitor cells<sup>177</sup>. Although these reports are encouraging, there has again been concerns raised about limited adherence of cells to the scaffolds<sup>178</sup>. Clearly, much work is still needed to consider tissue engineered heart valves a realistic alternative to current prostheses.

The potential benefits of this technology are massive and ensures that this is an attractive area of development which may or may not have a role in treating valvular heart disease in the future. This potential is hampered by the fear that the use of pluripotent cells have the potential risk to induce tumour formation. Although these concerns are primarily for embryonic stem cells, any pluripotent cell type could have this theoretical potential. This means that any usable prosthesis would require stringent safety testing procedures prior to clinical trials. The vast amount of investment into stem cell research makes the next few years extremely interesting but at present these valves do not jeopardise the future of the pericardial valve.

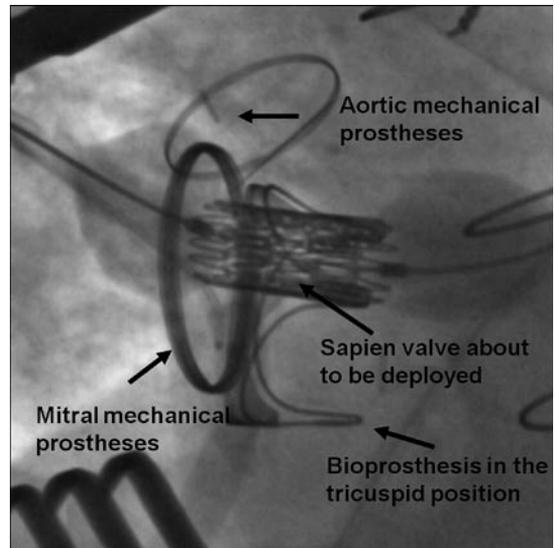
## The Future Of Alternative Delivery Methods For Pericardial Valves

### Transcatheter aortic valve implantation (TAVI)

The PARTNER trial has laid the foundations for the future of percutaneous valve replacement<sup>179</sup> providing evidence supporting a role in high risk surgical patients with aortic stenosis. The balloon expandable bovine pericardial Edwards Sapien valve and self-expandable porcine pericardial Medtronic CoreValve are the two TAVI devices in current use. On-going, randomised trials, for both the Sapien (PARTNER-2) and CoreValve (SURTAVI) are assessing outcomes in other populations of patients suffering from aortic stenosis, namely intermediate risk groups. Under particular scrutiny will be perioperative stroke rates which were shown to be higher in patients undergoing TAVI compared to conventional surgery. This will help define the future of TAVI further, and maybe provide justification for extending the indications of percutaneous aortic valve replacement over the next few years. In addition to aortic stenosis, percutaneous delivery of valves can be performed in

other settings including congenital valve disease. The bovine jugular vein Melody valves can be implanted in the pulmonary position<sup>180</sup> which has major potential benefits, in particular, for patients suffering from congenital heart disease. Extended indications for TAVI also include ‘valve-in-valve’ (Figure 7)<sup>181</sup> and ‘valve-in-ring’ TAVI<sup>182</sup> which is likely to increase over the next few years.

Whatever the indication for the use, the crux of whether percutaneous valve replacement ‘takes over the world’ will be the long-term outcomes. Currently, midterm outcomes only, are available, and although these are encouraging, whether the indications for TAVI valves become widened for routine use in low risk and younger patients is heavily dependent on whether durability is proven. This data is especially vital for percutaneous valves as the delivery mechanism has the potential to damage the prosthesis, potentially with long-term implications for structural degeneration. The crimping process can damage the valve<sup>183-184</sup> as well as the process of balloon expansion of percutaneous valves which can induce collagen disruption within the leaflets<sup>183</sup>. It is theorised, by some, that such damage may be less pronounced than in self expanding devices, but this remains to be seen<sup>185</sup>. At this stage, whether these experimental findings extrapolate into clinically significant structural valve degeneration is unknown, and will become apparent over the next decade. If outcomes are favourable, the use of the pericardial percutaneous valve prostheses will be assured in the modern, less invasive era of medical interventions.



*Figure 7: A ‘valve-in-valve’ TAVI procedure for stenosis of a prosthetic tricuspid valve, performed through the right atrium with cardiopulmonary bypass support.*

### Pericardial sutureless valves

With a general trend of adult cardiac surgical patients increasing in age and complexity with multiple comorbidities, a search for technologies aimed at exposing patients to less intrusive interventions is on-going. The potential of a less invasive approach aims at reducing the insult to the patient. This can theoretically allow effective treatment of high risk patients who were previously either reluctantly offered surgery, or thought to be too high risk for surgical correction of their valve dysfunction. TAVI is the obvious example of this less invasive approach but critics highlight that the gold standard treatment is still conventional valve surgery. A compromise between TAVI and conventional valve replacement is the sutureless valve, the use of which is now starting to become established. This technology has the potential to shorten the duration of procedures by enabling a limited excision of the native valve and avoiding the need for securing the valve with sutures and the associated ischaemic time<sup>186</sup>. In addition, the simplicity of this technology can enable less extensive incisions, as implantation can relatively easily be performed through mini-sternotomies which have been shown to reduce post-operative pain and improve post-operative respiratory function<sup>187</sup>. Additional potential benefits include reducing patient prosthetic mismatch due to the absence of a sewing ring and thus avoiding root enlargement procedures in elderly patients with small aortic roots<sup>188</sup>. One other potential benefit is,

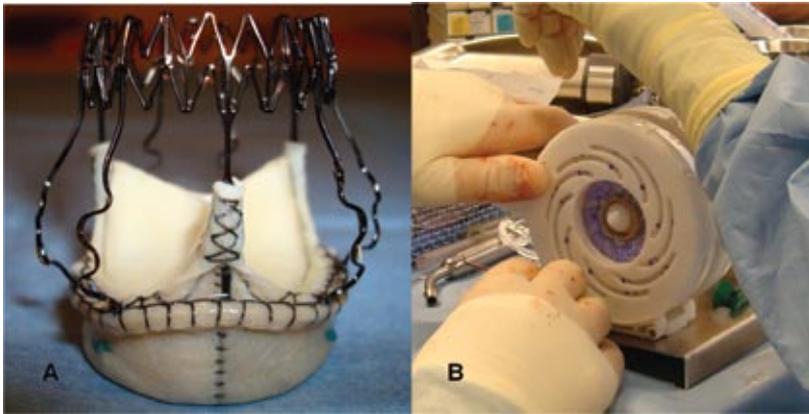


Figure 8:

A) Sutureless valve

B) Crimping device necessary for deployment of this valve.

by avoiding aggressive decalcification and also suture placement in the aortic annulus the post-operative pacemaker requirement could theoretically be lowered. In reality, this benefit may not be as marked, as some early series have still observed a need for pacemakers in a significant percentage of patients<sup>189</sup>.

Initial attempts at sutureless valves were problematic, with a high rate of paravalvular leaks being observed<sup>190</sup>. After this, they fell out of vogue but recently, numerous surgical series have championed this approach. Although, importantly, long-term results are not available, short to midterm results are encouraging. Certainly, the feasibility of the implantation of these valves in the aortic position have been shown<sup>191</sup> with good improvements in symptoms with low gradients and satisfactory effective orifice areas being achieved in series of well over a hundred patients<sup>192</sup>. Although randomised trials in this area are not available, propensity matching has shown that for sutureless valves, 30 day mortality is equivalent to conventional surgery and TAVI<sup>193</sup>. Experimentation is also starting to happen, as it did with TAVI, with early experience of expanding the indications being described. Redo aortic root procedures have been avoided by using sutureless ‘valve-in-valve’ implantation into failing stentless root biological prostheses<sup>194</sup>.

The sutureless valves are exclusively pericardial valves, either bovine or equine, which ensures this biological material is likely to have a healthy future. Concern does exist, however, about the long-term effects of crimping these valves, a process necessary for their deployment (Figure 8). Electron microscopy demonstrates how the damage<sup>195</sup> and mechanical stress of this nature can lead to changes within the valve leading to calcification of bioprostheses<sup>196-197</sup>, although not all reports agree<sup>198-199</sup>. Not only the crimping process, but also the balloon expansion of pericardial valves can lead to collagen fibre disruption<sup>200</sup>. Although, on the face of it, the enthusiasm for the future of the sutureless pericardial valve is well placed, the long-term results of this technology will be crucial in defining the true role of these prostheses. If fears over mechanical damage during the implantation process are realised, other potential materials may prove more appropriate. Such materials may include porcine vena cava valves which may have advantages over bovine pericardial valves as they are thinner and therefore have a superior profile. Their higher elastin content also means they potentially do not suffer as much damage during the crimping process<sup>201</sup>. The pericardial sutureless valve will therefore live and die by its long-term results.

## Conclusions

We have shown in this chapter that the future for the pericardial valve is extremely bright. We have discussed the general consensus to adopt biological instead of mechanical valve technology, as well as the consensus of surgeons to implant pericardial in preference to porcine bioprostheses. Both these observations are due to the superior haemodynamics of these valves as well as the overall reduced valve related morbidity. We have demonstrated that there are a variety of alternatives for treating valvular heart disease (valve repairs, homografts, autografts and stentless valves), which tend to be performed in high volume specialist centres, generally, with excellent outcomes. These alternatives are allowing the boundaries of cardiac surgery to be broadened and provide patients with more options. Although far from being experimental, they are mostly areas of cardiac surgery in which technique and technology are evolving, on an annual basis. However, for the majority of surgeons who work outside these specialist institutions, the pericardial valve will remain the mainstay of treating valvular heart disease, particularly for the aortic valve. The alternative delivery methods now available, in the form of percutaneous and sutureless technology, have cemented pericardial valves as the primary prosthesis of choice, at least for the foreseeable future. It is clear that long-term outcomes are necessary to fully commit to this conclusion, however, there is no doubt technology will move forward at a rapid pace in order to cope with any deficiencies that are identified. As Thomas Jefferson put it, “I like the dreams of the future better than the history of the past”.

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# Post Scriptum

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*To see a world in a grain of sand,  
And a heaven in a wild flower,  
Hold infinity in the palm of your hand  
And eternity in one hour.*

William Blake (1757-1827)

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The Society decided to publish the 'Odyssey of the Pericardial Valve' because this unique valve is the embodiment of a scientific concept of man-made heart valves, which was created and put into practice some 43 years ago here in Britain.

Although far from ideal, this valve became a paradigm, it is the valve accepted and elected by surgeons around the world as the best tissue heart valve available today.

The concept was elaborated and we began the implantation of the pericardial valves in Leeds in April 1971.

This book contains several scientific chapters, all of them clearly written and amply documented, taking the reader through the various steps of clinical usage and the improvement made to the original pericardial valve over the years.

It clarifies for the younger generation of cardiac specialists the origin of this concept and the way this British invention travelled across more than four decades of clinical use throughout the world.

The readers will discover, if they have not yet learned, the uniqueness of this concept and the reasons for its longevity and, I dare say, its favourable projection in the foreseeable future, or until the white wings of the Future will decide.

The clear and detailed description of the pericardial valve's various facets appears to me like an intellectual feast served to the readers by specialists, each one in their own domain. In addition to the description of clinical results and haemodynamic performance of this valve, the authors bring into focus two extremely important phenomena related to tissue heart valve replacement in general. These two groups of complications are thrombosis, embolism and haemorrhage, and the problem of tissue calcification. Both are complex and challenging phenomena, and the need for their better understanding and for further research and clarification is stressed.

This book refers also to the fact that the main useful change in the original pericardial valve was not made by surgeons but by commercial laboratories, which presented themselves as the progenitors of this original valve. These laboratories, and even some surgeons, try to make us believe that each of them discovered the 'Philosopher's Stone', unfortunately a habit too often encountered nowadays.

The continuation of the original dream, its perpetuation through the transcatheter aortic valve implantation - which progresses at a rarely encountered speed - is additional proof for the veracity and the vitality of the original man-made valve concept. To paraphrase Binder and Webb, one could say that - from the 'home-made' pericardial valve to the TAVI of today, the concept became a global surgical and interventional phenomenon.

Having had, myself, the chance to be involved in some search for a better way of looking at and dealing with heart valve surgery, I take this opportunity to address a few words to the younger surgeons, those who like me at that age, pretend to know everything about our imperfect world.

It would be useful to look at these two extremes to appreciate the divergent path in life: still waters are often deep and almost always have the colour of 'drowning', whereas discovering, inventing and, especially, creating something is like placing a smile on the human condition.

It seems that our entire experience as cardiac surgeons, when related to the notion of Time, unfolds between boredom and ecstasy. Inbetween these two extremes the choice is varied and infinite and for you, the season to choose is now.

Our forebears took us off the ground but who is going to keep us in flight?

I know that I could never teach anybody anything. All I can do is to show the direction towards a goal. I can give some of my memories but not my dreams or my thoughts, you have your own thoughts, you may see your own mark on the path to the mirage of the infinite in a different spot. We all have our own.

People often say that most interesting things were discovered or invented already and nothing was left to be done. The seeds of great discoveries are constantly floating around us but they only take root in minds well-prepared to receive them, as Joseph Henry used to say.

If you embark on such a venture you should be prepared to scatter many fragments of your spirit for the life of your idea. There will be many nights charged with the burden of your thoughts.

Often, alone and away from its nest, must the eagle fly across the sun.

Too often will the idea sail in your dreams, but in the end, maybe, your dusk will, in truth, become your dawn.

When the day of success, of harvest arrives, the following questions should still be asked: in what sort of fields and in what unremembered seasons have the seeds been sown and to which nameless people the fruit of your labours were offered?

In every enterprise of life there are usually two issues - you succeed or you fail. In fact, it is not important if you win or lose; the important thing is not to lose what you have won.

The final and essential thing for all young researchers is to truly believe in: *Audaces Fortuna Juvat*, and often she helps the audacious.

Marian Ion Ionescu

Monaco, June 2014





Society for Cardiothoracic Surgery in Great Britain and Ireland