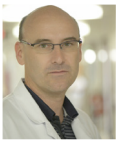

Lars Englberger

Brigitte Gansera

Tissue valve durability demonstrated by Enable® and Mosaic®

Tissue valves were first introduced more than 30 years ago. Following their introduction, considerable doubt remained regarding their durability. However, these valves have now gone through a number of iterations and data on two such valves, Enable® and Mosaic®, have shown that they are not only efficacious but also durable. *Confluence* spoke to Dr Lars Englberger, Department of Cardiovascular Surgery, University Hospital Berne, Switzerland about the 5-year Enable results and Professor Brigitte Gansera, Department of Cardiovascular Surgery, Clinic Bogenhausen, Munich, Germany about the history of over 17 years of Mosaic data.

What options are available for replacing diseased valves?

Dr Lars Englberger (LE): As surgeons, we have a variety of different heart valve substitutes available for the aortic position. We have traditional mechanical valves, and then going to the biological field we have stented and stentless values, we have special substitutes like homografts, and now a new sutureless valve.

What are the differences in those different valves? What are the pros and cons?

LE: Overall, mechanical valves are most often used in younger patients; however, since the results of biological valves and aortic positions are so good, these are now being used in younger and younger patients. In my personal opinion, sutureless valves are an excellent addition that enlarges our portfolio. This means that we have not only the stented or the stentless biological valves available, but also the sutureless valves, and it is really helpful to have these new valves available in our portfolio for specific patients. These include patients with a calcified aortic root or those who need redo surgery – when you have to replace, for example, a degenerative biological valve: those are the specific patients who will benefit most in the current era from sutureless valves. However, as people see good results with sutureless valves, especially the Enable® valve (Medtronic Inc., Minneapolis, USA), it is also possible that this technology may become the first choice in patients who have an indication for biologic aortic valve replacement.

Where do sutureless valves sit between traditional surgical valve therapies and transcatheter aortic valve implantation (TAVI)?

LE: The difference is still that we have regular open surgical access when we use sutureless valves, such as Enable. Quite often the sutureless valves are seen as competitors to TAVI valves; in my eyes this is not true. The sutureless valves, as I mentioned before, enlarges the portfolio of the cardiac surgeon and, looking to the future, will make minimal-access open surgery more feasible for the majority of surgeons and their patients. That means it helps, and the sutureless valves facilitate minimal-access surgery in aortic valve replacement. This can save time, which can be important in procedures where you expect longer or a technically difficult implantation process. For example, in mini-sternotomy access surgery for aortic valve replacement, sometimes it is challenging to place the valve; when you use a thoracotomy for the replacement of the aortic valve, in such patients, a sutureless placement makes this access more feasible.

Could you give us a brief history of sutureless valve technology?

LE: Sutureless valves were first proposed more than 30 years ago when the inventions were focussed on a mechanical valve anchored without sutures in the aortic annulus. Approximately 10 years ago, parallel to the development of the TAVI procedures, the technology to create a surgical valve that could be anchored without sutures became a realistic

prospect. As is the case in the Enable type of the sutureless valve, a regular, stentless biological valve with good results in the clinical setting, was combined with a self-expanding nitinol cage, and this made it possible to have a sutureless valve ready for the plantation.

Could you tell us a little bit about Enable and what makes it unique and different from other valves available?

LE: The uniqueness of Enable is that it is, first of all, made of equine pericardium, which is a good tissue – it is strong and comparable to bovine pericardium. In addition, the platform of the Enable development is a stentless and biological valve, which has shown good clinical results, the so-called "3f" valve (Medtronic, Inc., Minneapolis, USA). Despite good clinical results, the only problem with the 3f valve was, as for other sutureless valves, you have to implant it in the aortic root in an exact geometric fashion. It was, therefore, a good step to combine the 3f with a nitinol cage in Enable, because the geometry is given by the cage of the sutureless valve, enabling easier implantation.

Why are long-term data important for such valves?

LE: Traditional surgical aortic valve replacement procedures deliver excellent results and, therefore, new valve technologies must be at least at this level. This means that when you create or introduce a new valve in clinical practice, it must meet a number of requirements. Firstly, it has to be easy to be implanted and the introduction process should not be complicated. Secondly, the occurrence of paravalvular leaks when you implant sutureless valves should not be accepted. Thirdly, we must consider the durability of the valve. Because patients who undergo surgical valve replacement tend to be younger and at lower risk compared with TAVI patients, the valves need to last longer.

Can you tell us about the 5-year data for Enable?

LE: The 5-year follow-up of the first patients implanted with the Enable valve has recently been published in the *Journal of Thoracic and Cardiovascular Surgery*.[1] These data show excellent results from both haemodynamic and durability standpoints. We expected this though, because the platform of the Enable is the 3f stentless valve, which has also shown good haemodynamic results. In early patients, we see some paravalvular leakage, however, these problems were overcome or gone after a learning curve and, in addition, the 5-year data gives us confidence in the valve.

As I said, a new sutureless valve should not have any additional disadvantages when compared with the placement of current products. We see this with Enable and when – I believe in this – the sutureless placement of a valve is quick, safe and reproducible without a higher rate of paravalvular leak compared to standard, sutured valves, then it will really replace the old order sutured biologic valves in the future.

We have spoken quite a lot about some of the benefits of using sutureless technology, what are the limitations?

LE: While, ideally, the implantation process should be easy, this is not always the case when we have new devices in our hands as surgeons. Paravalvular leakage is still the major concern that we have had for all types of sutureless valves with a higher rate of paravalvular leaks and placement problems; however, the flow characteristics we have with the Enable valve appear to be very encouraging.

Please can you briefly outline the Mosaic valve and describe for which indications, and in which patients, it should be used?

Professor Brigitte Gansera (BG): The Mosaic® (Medtronic, Inc., Minneapolis, USA) valve is a third-generation porcine bioprosthesis secured to a cloth-covered flexible stent for support, combining several new features to improve haemodynamics and durability. These features include a low profile stent for reduced flow obstruction, zero pressure fixation to maintain the natural collagen crimp, and the amino oleic acid anti-mineralization treatment to enhance durability.

The Mosaic valve is normally used to replace a stenosed aortic valve; severe calcification is not an obstacle to use for the Mosaic valve. While Mosaic valves have traditionally been implanted in patients over 65, today we are increasingly seeing their use in younger patients (>55 years), who do not want to be placed on long-term warfarin therapy (which would be the case with mechanical valves). The Mosaic valve can be implanted in supra-annular or intra-annular positions. If the supra-annulus position is preferred, the entire bioprosthesis can be seated superior to the annulus allowing for use of larger bioprostheses. The Mosaic valve has been shown to provide excellent haemodynamic results

in higher diameter valves (25/27/29 mm) and good haemodynamic profiles in the smaller annular sizes (21/23 mm); however, all bioprosthetic valves show similar haemodynamic flow.

I was involved in the first implantation of a Mosaic valve in the initial trial for the device in February 1994. A number of studies supported the introduction of the Mosaic valve[2-5] and demonstrated that these valves are efficacious and have favourable safety profile with low rates of valve associated complications; excellent long-term durability has been demonstrated by the recent release of the 17-year data.[6]

In the long-term, Mosaic appears to be more durable than earlier generation tissue valves. What features of the Mosaic valve account for this longevity?

BG: Two key technologies offer differentiation from other tissue valves on the market and contribute to the long-term durability of the valve, the alpha amino oleic acid treatment and a Fixation process. The cross-linking of the porcine aortic root tissue is accomplished using a Physiologic Fixation process, whereby hydrostatic pressure is applied to the root while maintaining a zero pressure differential across the valve leaflets; this helps to maintain the natural leaflet form and function. The alpha amino oleic acid tissue treatment has been shown to result in significant reductions in mineralization (primarily calcification) on the valve.

Can you please give us an overview of the key clinical trials that support the use of the Mosaic valve, including the 17-year data?

BG: Our first study compared 55 Mosaic valves, implanted in the aortic position since February 1994 (group 1) with data from 52 patients who had received a Hancock Modified Orifice II aortic valve (group 2).[4] The mean patient age was 72.0±5.9 years for group 1 and 76.8±4.7 years for group 2. Clinical examinations including transthoracic echocardiography were performed at 6 and 24 months post-operatively. In the 2-year follow-up, haemodynamic measurements showed mean pressure gradients of 12.4 mmHg for the 21 mm, 11.3 mmHg for the 23 mm, and 15.4 mmHg for the 25 mm prostheses in the Hancock group.

In the Mosaic group, mean pressure gradients were 14.8 mmHg for the 21 mm, 10.9 mmHg for the 23 mm, and 11.5 mmHg for the 25 mm valves. Differences between pressure gradients and effective orifice areas of the Hancock and the Mosaic valves were not statistically significant. The Mosaic valve has low pressure gradients for all sewing ring diameters. Compared with the Hancock Modified Orifice valve, there was no statistically significant gradient difference but a tendency toward better haemodynamics was noted in the Mosaic group after 2 years.

Another initial trial consisted of 100 patients followed-up prospectively, within the initial hospitalization for valve replacement, 6 months post-operatively and at annual intervals including an haematological check and transthoracic echocardiography.[2] The mean follow-up was 2.7 years with a total follow-up of 273.7 patient years. The follow-up was 100% complete. After 5 years, the mean systolic pressure gradient was 15.2±3.0 mmHg for the 21 mm, 13.1±4.6 mmHg for the 23 mm, 10.0±3.1 mmHg for the 25 mm valve size, while the effective orifice areas were 1.6±0.3 cm^2 (21 mm), 1.9±0.3 cm^2 (23 mm) and 2.5±0.8 cm^2 (25 mm). The freedom from prosthesis-related event rates, calculated according to Kaplan–Meier, at 5 years were: 97.3±1.9% for permanent neurological, 99.0±1.0% for transient neurological, 95.9±3.2% for thrombosed prosthesis, 95.6±2.2% for anti-thromboembolic related haemorrhage, 96.2±3.7% for structural valve deterioration, 96.9±3.0% for non-structural dysfunction, 100% for endocarditis and 92.0±4.9% for explant. The late post-operative mortality was 4.4% per patient year and included a valve-related mortality rate of 0.7%/patient year. In relation to other biological prostheses (Intact, Carpentier-Edwards Pericardial and Porcine, Hancock Modified Orifice, Biocor, Freestyle), the Mosaic bioprosthesis showed very satisfactory and predominantly better haemodynamic results than the compared stented valves and approached the performance of stentless prostheses.

The freedom rates from prosthetic-related adverse events of the Mosaic bioprosthesis were at least equivalent to the compared prostheses.[5] Follow-up of these 100 patients at 7 years was published by our group in 2003.[5] Mean follow-up was 3.8 years (range: 0.1–7.1 years); total follow-up was 383.1 patient years (pt yr) and 100% complete. Late mortality was 4.6%/pt yr, including a valve-related mortality of 0.6%/pt yr. Freedom from event

at 7 years was 96.8±1.8% for thromboembolic events, 97.2±2.0% for thrombosed bioprosthesis, 96.6±2.6% for structural valve deterioration, 98.2±1.8% for non-structural dysfunction, 95.9±2.0% for anti-thromboembolic haemorrhage, 98.9±1.1% for endocarditis, and 93.9±3.2% for reoperation/explant. After one year, the mean systolic pressure gradient was 15.3±6.7, 14.5±5.7, 12.7±4.1 and 12.9±4.8 mmHg for 21, 23, 25 and 27 mm valves respectively; the effective orifice area was 1.4±0.4, 1.7±.0.4, 1.8±0.4 and 2.6±0.4 cm^2 for 21, 23, 25 and 27 mm valves respectively; and the effective orifice area index was 0.8±0.3, 0.9±0.2, 0.9±0.2 and 1.3±0.1 cm^2/m^2 respectively. The mean left ventricular mass index was decreased significantly, from 159.7±56.8 g/m^2 to 137.3±40.8 g/m^2, for all valve sizes after one year. In summary, clinical and haemodynamic performance of the Mosaic bioprosthesis was highly satisfactory during the first seven years after clinical introduction.

Celiento et al. confirmed excellent long-term results in 178 patients after 13 years.[7] Prosthetics of sizes 23 mm were implanted in 98 patients and 25 mm were used in the remaining 66. Follow-up was completed in December 2009 with a cumulative duration of 1,015 patient/years (mean, 5.7±3.5 years, maximum, 13.7 years). Early mortality was 4%, none being valve related; of 38 late deaths, 7 were valve-related. Survival at 13 years was 48±8%. Mean functional class of current survivors was 1.2±0.6. Six embolic episodes occurred and four cases of endocarditis, with respective actuarial freedom of 92±5% for embolism and 97±2% for endocarditis at 13 years. Four patients required reoperations for endocarditis and 2 for structural deterioration. Freedom from structural deterioration and from reoperation for all causes was 89±7% and 86±7% at 13 years, with freedom from prosthesis-related deaths of 86±5%. Results of echocardiographic evaluation at 1 year were mean peak gradient, 20±6 mmHg and mean effective orifice area index, 1.07±0.21 cm^2/m^2 for size 23 mm and 22±6 mmHg and 1.11±0.26 cm^2/m^2 for size 25 mm; at 10 years, mean peak gradient and mean effective orifice area index were 28±13 mmHg and 1.01±0.19 cm^2/m^2 for size 23 mm and 26±8 mmHg and 1.08±0.18 cm^2/m^2 for size 25 mm. This study underpins our own experience with the Mosaic bioprosthesis and showed good overall performance, with low incidence of structural valve deterioration and haemodynamic stability in the long term.

Riess et al. demonstrated excellent clinical performance and safety of the Mosaic bioprosthesis (mitral and aortic position) after 13 years of follow-up.[8] This prospective, non-randomized trial included 255 patients with aortic valve replacement (AVR; mean age: 67 years, range: 23–82 years) and 47 patients with mitral valve replacement (MVR; mean age: 67 years, range: 41–84 years). Follow-up visits were performed 30 days and 6 months after implant and annually thereafter. The cumulative follow-up was 1976.2 pt yrs after AVR (median: 8.3 years, maximum: 14.0 years) and 336.9 pt yrs after MVR (median: 8.2 years, maximum: 13.3 years). After AVR, mean systolic gradient and effective orifice area at 4, 8 and 13 years follow-up were 13.3±5.6, 15.5±7.7 and 16.0±7.2 mmHg and 1.8±0.5, 1.8±0.5 and 1.7±0.4 cm^2. After MVR, respective data were 4.7±2.1, 4.3±1.2 and 5.0 mmHg (only one recording) and 2.2±0.7, 2.3±0.6 and 1.8 cm^2. Transvalvular regurgitation at 13-year follow-up was mild or less in both the AVR and MVR patients. Thirteen-year survival was 63.1±4.5% in the AVR group and 51.2±13.6% in the MVR group. Early mortality after AVR and MVR was 1.2% and 0.0%, respectively; late mortality was 3.2%/pt yr and 3.3%/pt yr, including a valve-related/unexplained mortality of 1.1%/pt yr and 0.9%/pt yr. Freedom from adverse events in the AVR and MVR group was permanent neurological event: 97.4±1.2% and 96.0±3.9%; valvular thrombosis: 97.8±1.1% and 100%; structural valve deterioration: 84.8±7.8% and 93.8±6.1%; explant: 73.3±7.3% and 89.3±6.5%.

One of the largest follow-up studies for the Mosaic bioprosthesis including a 12-year follow-up (mean 7.5 years) of 797 patients receiving AVR was carried out by Jamieson et al. in 2011.[9] Freedom from valve-related mortality and reoperation was 87.1±3.1% and 84.0±3.3%, spectively, for AVR at twelve years. Freedom from structural valve deterioration (SVD) by explant reoperation at 12 years for AVR was 93.3±2.6% for patients at least 60 years old and 75.9±9.3% for patients younger than 60 years. Haemodynamic performance data at 1 year for AVR (sizes 21–27 mm) were mean systolic gradient range 13.7±4.8 to 10.3±3.2 mmHg and effective orifice area range 1.5±0.3 to 2.5±0.4 cm^2.

In conclusion, this study, involving a large patient population, could demonstrate that overall

performance of the Mosaic porcine bioprosthesis to 12 years was satisfactory.

Our recently published own data, concerning long-term (17 years) results[6] in 272 patients with isolated AVR in the aortic position provided evidence for very satisfying long-term outcomes after AVR with the Mosaic bioprosthesis. Incidence of valve-related complications or need for reoperation due to SVD was low.

With the advent of transcatheter aortic valve replacement (TAVR), surgeons have had to alter their decision-making process for surgical implantation. How does Mosaic fit into this decision if a patient requests future TAVR intervention?

BG: This is an increasingly important topic for our ever-younger patients who may have failing valves as they approach later life. Valve-in-valve implantation represents a minimally invasive alternative to surgical valve re-replacement in elderly high-risk patients with bioprosthetic structural valve deterioration. The Mosaic valve offers significant advantages for future valve-in-valve implantation compared with stentless bioprostheses and I have seen excellent results in my clinical practice using this valve. It has radio-opaque markers that help to facilitate correct transcatheter valve positioning during valve-in-valve implantation, while stentless bioprostheses may not have sufficient calcification to determine annulus location. In TAVI imaging modalities, TEE, and CT imaging are essential for determining anatomic suitability of valve-in-valve implantation; bulky leaflet calcification and pannus in degenerated bioprostheses can be identified to avert procedural complications. Coronary angiograms or coronary CT scans are critical for both TAVI and valve-in-valve. Unlike most bioprostheses, Sorin Mitroflow (Sorin, Vancouver, BC, Canada) and St Jude Trifecta (St Jude, St Paul, MN) have leaflets mounted outside the stent to maximize orifice area. During valve-in-valve implantation, these bioprosthetic leaflets, not being constrained within stent frame, may extend to aortic wall and potentially obstruct coronaries. Aortic root anatomy, coronary ostial position, and specifics of the bioprosthesis are important considerations for valve-in-valve implantation to avoid coronary obstruction. Particularly, the relationship of the bioprosthetic stent and leaflet height in relation to coronary orifices and size of sinotubular junction should be noted by CT scan before intervention.

One key difference between valve-in-valve implantation and TAVI is the presence of radiopaque markers in most stented bioprostheses. Mosaic and Hancock valves have 3 small radiopaque rings at the top of struts, but in addition, the Hancock has a radiopaque sewing ring. Carpentier-Edwards bioprostheses have a visible annular and strut frame. The sewing ring of the Mitroflow is also radiopaque but the St Jude bioprostheses have a faintly radiopaque annulus that requires high-resolution imaging. Overall, the ability to see stented bioprostheses fluoroscopically is a significant advantage by providing an ideal landmark to facilitate correct THV positioning. Stentless bioprostheses and homografts are similar to native aortic valves, in which leaflet calcification provides the landmark for positioning. However, when the failure mode is regurgitation, stentless valves may be more challenging than native valves because sufficient calcification may not be present to determine annulus location.

For years, the surgical community has held the belief that pericardial valves are more durable. Do you feel that this belief about pericardial durability is based more on marketing than clinical data?

BG: PERIMOUNT (Carpentier-Edwards) has very similar durability and that there is actually very little difference in this area.[7-13] However, the pricing of tissue valves, such as Mosaic, mean that I feel they offer an attractive proposition in comparison to biomechanical valves.

It's also been a common misnomer that porcine valves have higher gradients, however the LVMR is the same. Your data, along with several others, have shown that Mosaic gradients remain stable over time. What do you believe plays into its longevity?

BG: Data have shown that the Mosaic maintains its haemodynamic gradient with excellent consistency throughout the life of the product. This is likely due to the design of the product, the Physiologic Fixation process and alpha amino oleic acid tissue treatment.

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What does the future look like for tissue valves such as Mosaic?

BG: These valves already offer an excellent level of performance, safety and durability, and have already benefited many patients. Subsequently, I do not feel there is much more that is required in terms of development of these products at present.

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DISCLOSURES: BG has no disclosures or conflict of interests relating to this article. LE received speaker fees from Edwards Lifesciences, Sorin, and Medtronic, Inc. He received honoraria for proctoring and consultancies from Medtronic, Inc.