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Trans-catheter valve-in-valve implantation: *in vitro* hydrodynamic performance of the SAPIEN + cloth trans-catheter heart valve in the Carpentier-Edwards Perimount valves☆

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Abstract

Objective: Since 1990, over 1.2 million bioprosthetic valves were implanted for aortic stenosis. Given the risk of structural valve deterioration, the need to redo AVR will likely rise. Recently, SAPIEN valve-in-valve (ViV) has been advocated. We evaluated the *in vitro* hydrodynamic performance of the Edwards SAPIEN + cloth trans-catheter heart valve (THV) implanted within the Carpentier-Edwards Perimount (CEP) valve. **Methods:** Both 23- and 26-mm Edwards SAPIEN + cloth THVs (Model 9000MIS) were deployed within 23- or 25-mm (1) CEP aortic bioprosthesis (Models 2700 and 2800), (2) CEP Magna (Model 3000), and (3) CEP plus pericardial mitral (Model 6900P), respectively. Tests included: (1) mean pressure gradient; (2) pulsatile effective orifice area (EOA); (3) regurgitant volume; (d) migration during accelerated wear testing (AWT; 20 million cycles @ 200 mmHg); and (5) valve dislodgement pressure. Values tested per ISO 5840:2005 valve standards; mean $\pm$ SD. **Results:** Post-deployment pressure gradient across the combined valves ranges from 2.8 ± 0.3 to 8.7 ± 0.5 mmHg. The post-deployment EOA of the valves ranged from 1.7 ± 0.1 to 2.0 ± 0.0 cm^2. Pulsatile flow regurgitant volume ranged from 2.1 ± 0.7 to 7.6 ± 1.2 ml. Migration during the AWT ranged from 0.01 ± 0.27 to 1.61 ± 0.92 mm. Pressure increase during the tests to quantify migration ranged from >400 to >800 mmHg. **Conclusions:** Compared with the rigorous ISO 5840:2500 valve standards, the Edwards SAPIEN + cloth THV implanted ViV within the CEP valve demonstrated excellent hydrodynamic performance.
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Keywords: Aortic valve replacement; Valve-in-valve (VinV) implantation; Trans-catheter; Trans-apical; Minimally invasive

1. Introduction

An increasing number of patients are living with surgically implanted valves that no longer provide an acceptable quality of life. Previous valve-in-valve studies have shown that deploying a trans-catheter valve in a degenerative bioprosthetic valve is a practical solution; however, the data available are limited and more studies have to be performed to ensure compatibility between the degenerative valve and the selected trans-catheter replacement valve.

The current valve-in-valve study is focused on the use of an Edwards SAPIEN™ trans-catheter heart valve (THV) cloth valve (see Fig. 1), which is identical to the SAPIEN model, but has an added outer cloth for implantation into a degenerative bovine pericardium, Carpentier-Edwards Perimount (CEP) bioprosthetic valve. The CEP surgical valves are made with a base that is more rigid than other valves. When a SAPIEN™ valve is expanded in the CEP valve, the rigid base does not easily conform to the profile of the expanded stent frame, which leaves gaps between the two valves, resulting in higher paravalvular leak. The addition of an outer cloth to the SAPIEN™ cloth valve is designed to reduce paravalvular leak by creating a seal between the two valves and improve resistance to migration with better 'fit' within surgical Perimount valves.

Why is the outer cloth required?

- reduce paravalvular leak;
- increase 'fit' within EW surgical Perimount valves; and
- promote tissue ingrowth, which further decreases paravalvular leakage.

The current study aims to verify that the 26-mm cloth valve is resistant to significant migration when deployed in the 25-mm surgical valve.

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Edwards v. Aortic Innovations
U.S. Patent 11,491,033
Edwards Ex. 1007

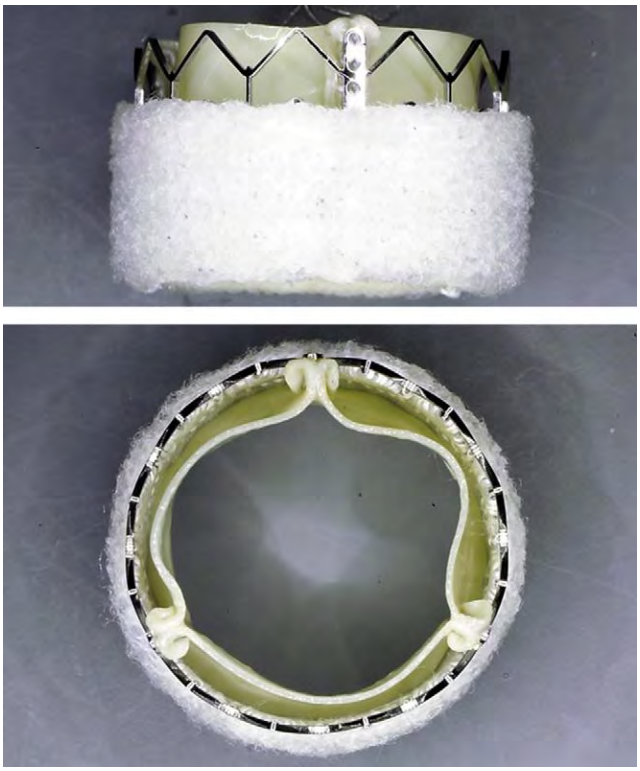

Fig. 1. Cloth valve.

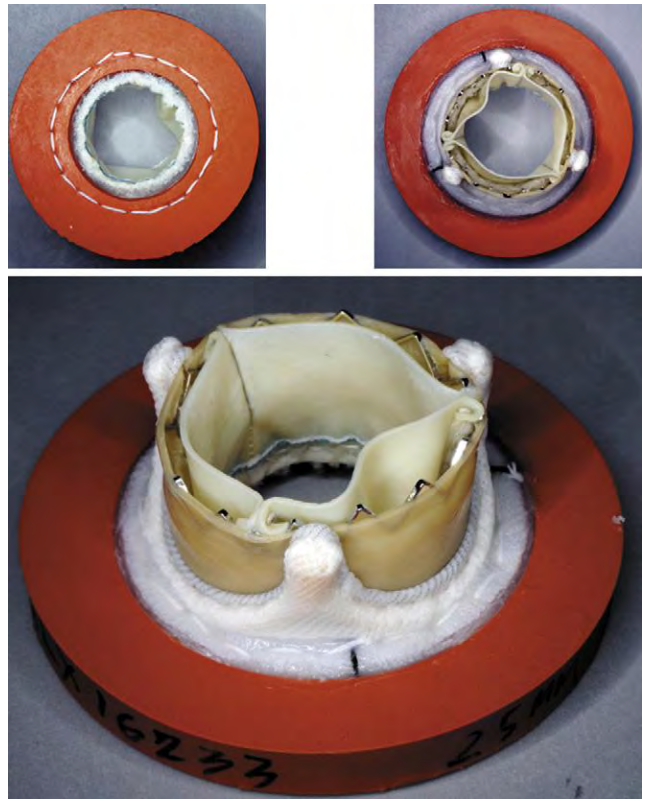

Fig. 2. Cloth THV valve deployed in surgical valve.

2. Methods

Bench-top testing specific to the valve-in-valve application was carried out on SAPIEN™ cloth valves. An added poly(ethylene terephthalate) (PET) cloth was stitched onto the perimeter of each SAPIEN valve. The SAPIEN valves were deployed inside various CEP valves (see Figs. 2 and 3) via the 33F Ascendra system. Resultant valve combinations were then subjected to hypertensive conditions during hydrodynamic testing followed by 20 million cycles of hypertensive accelerated wear testing (AWT).

Migration measurements were taken after exposure to the following conditions:

- 300 mmHg steady back pressure;
- 30 ml min^{-1} forward flow;
- normotensive pulsatile ($\Delta p = 100 \pm 5$ mmHg);
- hypertensive pulsatile ($\Delta p > 210$ mmHg); and
- hypertensive AWT for 20 million cycles (6 months).

After 6 months, tissue ingrowth helps secure the valve in place; therefore, the first 6 months (20 million cycles) represent the worst case for potential valve migration. The testing for resistance to migration is summarized in the test specimen flow chart shown in Fig. 4.

2.1. Pre-test inspection

The cloth valve is inspected, measured, and digitally photographed before being prepared for valve-in-valve deployment. Any damage to the leaflets, sutures, or cloth of the cloth valve or CEP valves is recorded.

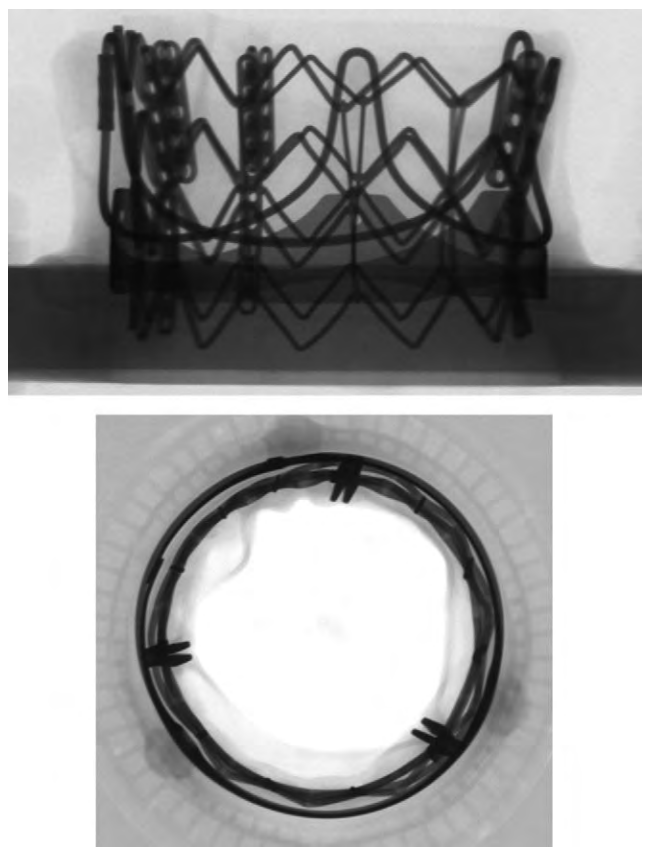

Fig. 3. X-ray images taken during test for migration.

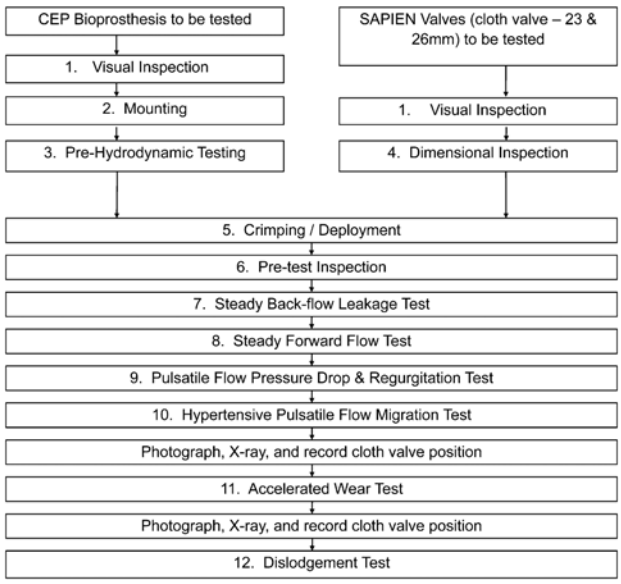

Fig. 4. Valve-in-valve testing flow chart.

2.2. Valve mounting

The CEP bioprosthetic valves were mounted with sutures onto 1/4 in. thick $\times$ 2 in. diameter rubber gaskets and sealed with Dow Corning Silastic® medical adhesive. The valve serial number is recorded on the rubber gasket to ensure traceability. The valve sewing ring is attached to the silicone disk by mattress-type sutures around the entire circumference, and the porous fabric is also sealed with the Dow Corning Silastic® medical adhesive on the inflow and outflow sides of the valve. These valves are then put in a buffered saline solution for 24 h to allow the adhesive to cure. The commissure number is identified by marking on the rubber gasket.

The sealing is verified by performing a static leak test. The sealing of the valve is considered completed once the result from the static leakage test is less than 200 ml min^{-1} at 100 mmHg.

All valves are photographed (inflow, outflow, and side views) after mounting onto the gaskets. In addition, the valves are X-rayed with the outflow pointing away from the X-ray source, and from the side after mounting.

2.3. Valve-in-valve expansion

The test cloth valves are expanded and positioned within the CEP bioprosthetic heart valve such that the bottom of the frame of the cloth valve is 2 $\pm$ 2 mm below the bottom of the surgical valve. The following is recorded:

- the peak balloon inflation pressure required to expand the cloth valve within the bioprosthetic valves is recorded with a pressure gauge attached to the balloon inflation port;
- the measurements of the outer diameters at the outflow of the deployed cloth valves are recorded;
- the time to inflate/deflate the balloon is recorded; and
- relative positioning of the cloth valve to the CEP bioprosthesis is observed and recorded (initial position for migration test).

Positioning is recorded by measuring the distance between the tip of the CEP bioprosthetic valve wireform commissures relative to the tip of the cloth valve frame. Detailed photos and X-ray inspections of all valve-in-valve test articles are performed before and after hydrodynamic testing. The position of the cloth valve relative to the surrounding CEP bioprosthesis is recorded before each visual/X-ray inspection to evaluate migration.

2.4. Steady backflow leakage test

The objective of the steady backflow leakage test is to assess the cloth valve's resistance to migration under steady backflow pressures when deployed in the valve-in-valve configuration. Relative movement of the cloth valve within the CEP bioprosthetic heart valve is recorded. Backflow measurements, in ml s^{-1}, are measured for the valves at steady back pressures of 100 $\pm$ 5, 200 $\pm$ 5, and 300 $\pm$ 5 mmHg. A total of five measurements per pressure per valve were recorded. The test fluid used is phosphate buffered saline solution at ambient temperature.

2.5. Steady forward flow test

The Steady Forward Flow Test applied a pressure gradient across the valve at forward flow conditions. The objective is to test the cloth valves' resistance to migration in valve-in-valve configurations under forward flow. Test valves are positioned between the inflow and outflow valve chamber sections of the test system and exposed to forward flow rates. A standardized nozzle to characterize forward flow per ISO 5840 is used as a reference to characterize and verify the test system. Five pressure drop readings are measured at one flow rate of 30 l min^{-1} and the average calculated. The test fluid is phosphate buffered saline solution at ambient temperature.

2.6. Pulsatile flow pressure drop and regurgitation

The pulsatile flow test determines average pressure drop, effective orifice area (A_{EO}), and regurgitation of the valve-in-valve configuration (cloth valve and the respective CEP bioprosthetic heart valve) under simulated physiological pressures and flow rates. A_{EO} is evaluated and compared with requirements described in ISO 5840:2005, section 7.2.3.

For this *in vitro* study, the paravalvular leakage between the CEP bioprosthesis and model cloth valve interface is not representative of the clinical environment because there is no tissue overgrowth on the CEP bioprostheses; therefore, the total regurgitation that was recorded is for information only. No acceptance criteria were set for the regurgitation in this study. Total regurgitation consists of the combination of central regurgitation of the cloth valve and paravalvular leakage between the cloth valve and the CEP bioprosthesis. The SAPIEN valve, which is similar in construction and design to the cloth valve, except for the attachment of the outer cloth, has demonstrated acceptable *in vitro* central regur-

gitation performance and meets the ISO 5840:2005 section 7.2.3 standard for minimum performance requirements. The total regurgitation, including central and paravalvular components for the valve-in-valve combination, will be evaluated within an *in vivo* validation study.

The test fluid is phosphate buffered saline solution at ambient temperature. Before initial data measurement, the test set-up is run for 10 min so that the valve-in-valve configurations may settle.

All test samples with the CEP bioprosthetic valves were tested at the simulated aortic cardiac output conditions listed in Table 1. The cloth valve mounted within aortic CEP bioprostheses was positioned between the inflow and outflow sections of the aortic valve chambers of the Inpulse Cardiac Pulse Duplicator.

Ten cardiac cycles were used to acquire and analyze data and the following parameters were reported:

- mean pressure difference across the test valve;
- effective orifice area (A_{EO});
- mean and rms flow rate;
- cycle rate;
- mean arterial pressure over the whole cycle;
- duration of forward flow through the test heart valves, as a percentage of cycle time;
- stroke volume;
- regurgitation volume, including the closing, leakage, and total regurgitation volumes and corresponding mean pressure difference across the closed valve; and
- regurgitant fraction including the closing, leakage, and total regurgitation fraction and corresponding mean cardiac output.

2.7. Hypertensive pulsatile

The purpose of this test was to put the test valve samples through hypertensive conditions for 10 min to test for resistance to migration. The test fluid is phosphate buffered saline solution at ambient temperature.

The position of the cloth valve relative to the surrounding CEP bioprosthesis and photograph/X-ray was recorded before and after the hypertensive pulsatile testing.

The test valves were positioned between the inflow and outflow aortic valve chambers of the inpulse duplicator. The test valves were tested for 10 min at the simulated cardiac output conditions listed in Table 2.

2.8. Hypertensive AW

Detailed visual/X-ray inspection and measurement of the relative position of the cloth valves inside their respective CEP bioprosthesis were performed prior to initiation of accelerated pulsatile testing for all valve-in-valve test items. The test items were then mounted on AWT testers to evaluate resistance to migration under the following conditions:

Test conditions for AWT:

- cycle rate: 1000—1400 cycles per min;
- minimum duration: 20 million cycles;
- test solution: phosphate buffered saline solution with Kathon CG/ICP;
- temperature: ambient temperature;
- ninety-five percent of the pressure cycles shall be above 185 mmHg for aortic and 210 mmHg for mitral (Stage 4, very severe hypertension).

A description of the fluid used for the assessment, including its biological origin or chemical components, temperature, viscosity, pH, and specific gravity, was recorded as specified in ISO 5840:2005 Annex M. To ensure that the minimum peak pressure difference of 185 mmHg for aortic and 210 mmHg for mitral (Stage 4/very severe hypertensive pressure per ISO 5840:2005 section 6.2.1) is established and maintained for 95% of the test cycles, the peak differential pressure during valve closing was targeted 20 mmHg higher (205 mmHg for aortic and 230 mmHg for mitral). Pressure signals were acquired for 10 cycles every other day. At each pressure data acquisition, the variable and physical observations of the valves were recorded and attached to the final report.

The AWT tester was set up and tuned to obtain a valve opening similar to that seen in the pulse duplicator. If valves became incompetent due to significant migration or if the specified differential pressures could not be maintained, the valves were removed from the testers prior to completion of the study. All valves were photographed and X-rayed after they had completed 20 million cycles or at the time of removal due to failure. The final relative positions of the cloth valve within their respective CEP bioprosthesis were measured.

2.9. Dislodgement test

A dislodgement test was performed to measure the amount of pressure needed to dislodge the cloth valve from the surgical valve. The test was run on the back pressure leakage tester, which maintains a steady continuous pressure gradient over a closed prosthetic valve. The pressure gradient is increased at increments of 100 mmHg and left at the pressure for 1 min to check if the cloth valve is dislodged. If the cloth valve is not dislodged then the pressure is increased 100 mmHg and held for 1 min again to check for dislodgement. This process continues until the cloth valve is dislodged or the highest pressure gradient attainable by the tester is achieved. The final test pressure was then recorded for each valve-in-valve test article. These final dislodgement test pressures are listed in Table 3.

Table 1. Simulated cardiac output conditions at normotensive conditions per ISO 5840:2005 (E) standard.

Cycle rate (bpm)	Aortic forward flow ratio (%)	Cardiac output (l min^{-1})	Arterial pressure		
			Mean (mmHg)	Systolic (mmHg)	Diastolic (mmHg)
70 ± 1	35 ± 2	5.0 ± 0.1	100 ± 5	125 ± 20	80 ± 20

Table 2. Simulated cardiac output conditions for valves at hypertensive pressures per ISO 5840:2005 (E) standard.

Test condition	Cycle rate (bpm)	Mitral forward flow ratio (%)	Simulated cardiac output (l min^{-1})	Mean pressure difference across the closed valve (mmHg)
1. Aortic CEP models	70 ± 1	60 ± 2	5.0 ± 0.1	185 ± 5 (very severe hypertension)
2. Mitral CEP models	70 ± 1	60 ± 2	5.0 ± 0.1	210 ± 5 (very severe hypertension)

3. Results

Before valve-in-valve deployment, the sealing and mounting of the CEP bioprosthetic valves was checked with the Steady Back Flow Leakage Test to confirm that there were no co-aptation issues or gross leakage between the CEP valve and the mounting gasket. All of the CEP valves were shown to have acceptable leakage prior to cloth valve initial valve deployment into their respective bioprosthetic valves. The cloth valves were positioned within the CEP bioprosthetic heart valves such that the bottom of the cloth valve frame (inflow) is 2 ± 2 mm below the base of the CEP. The relative positions of the cloth valves were recorded and methods documented in R&D lab notebook. The height measurements describe the distance between the outflow end of the cloth valve frame aligned with the tip of the CEP valve commissures. The diameter measurements were measured at the outflow sections of the cloth valves at the three cloth valve commissures. The architecture of the inflow section of the CEP valves did not make it possible to measure the inflow sections of the cloth valves. The diameters after deployment showed a range of values that fall within the specification for THV deployment size. For this *in vitro* study, the paravalvular leakage between the CEP bioprostheses and cloth valve interface is not representative of the clinical environment because there is no tissue ingrowth in the CEP bioprostheses; therefore, the total regurgitation was recorded for information only. No acceptance criteria were set for the regurgitation in this report. Total regurgitation consists of the combination of central regurgitation of the cloth valve and paravalvular leakage between the cloth valve and the CEP bioprostheses. The cloth valve, which is similar in construction and design to the SAPIEN valve except for the attachment of the outer cloth, has demonstrated acceptable *in vitro* central regurgitation performance in previous verification studies, meeting minimum performance requirements standard per ISO 5840:2005 section 7.2.3. The total regurgitation including central and paravalvular components for the valve-in-valve combination will be evaluated within an *in vivo* validation study. After pulsatile testing, the valve-in-valve relative distances were measured again. For reference, the initial deployment relative distances were subtracted from the position measured after pulsatile testing, to determine if the valve had migrated after exposure to hypertensive conditions. All valve combinations were then exposed to at least 210 mmHg pressure differences

Table 3. SAPIEN cloth valve-in-valve resistance to migration.

Sample	Hypertensive test condition: Δp (mmHg)	Migration after 20 million cycles hypertensive AWT (mm)	Dislodgment pressure (mmHg)	Model
1	218 ± 15	−0.09	>800	2700
2	221 ± 11	0.05	>800	2700
3	223 ± 7	0.16	>800	2700
4	230 ± 10	−0.13	>800	2700
5	230 ± 17	0.18	>800	2700
6	236 ± 18	0.06	>800	2700
7	225 ± 15	0.10	>800	2800
8	221 ± 14	−0.08	>800	2800
9	225 ± 21	−0.32	>800	2800
10	210 ± 11	0.26	>800	2800
11	215 ± 9	0.16	750	2800
12	215 ± 9	0.12	700	2800
13	213 ± 7	−0.13	600	3000
14	227 ± 14	0.19	800	3000
15	214 ± 7	0.45	800	3000
16	222 ± 12	2.66	500	6900P
17	237 ± 17	1.18	500	6900P
18	224 ± 15	0.98	700	6900P
19	244 ± 13	−1.34	[a]	6900P
20	237 ± 9	−0.61	[a]	6900P
21	236 ± 7	−1.20	[a]	6900P
22	247 ± 15	0.16	[a]	2700
23	257 ± 11	0.38	[a]	2700
24	226 ± 10	−0.15	[a]	2700
25	259 ± 17	−0.25	[a]	2800
26	245 ± 13	−0.04	[a]	2800
27	249 ± 15	−0.15	[a]	2800
28	227 ± 5	0.20	[a]	3000
29	231 ± 8	0.08	[a]	3000
30	243 ± 9	−0.31	[a]	3000

[a] Test articles were not tested for dislodgement because they are to be used in other long term tests.

Table 4. Valve-in-valve combinations.

Edwards bioprosthetic model	Cloth valve (33F delivery)	
	23 mm cloth valve	26 mm cloth valve
Carpentier-Edwards Perimount Model 2700	23 mm	25 mm
Carpentier-Edwards Perimount Model 2800	23 mm	25 mm
Carpentier-Edwards Perimount Model 2900[a]	23 mm	25 mm
Carpentier-Edwards Perimount Magna Model 3000TFX	23 mm	25 mm
Carpentier-Edwards Perimount Model 6900P	N/A	25 mm

[a] For the purposes of valve-in-valve deployment, model 2800 and model 2900 can be considered equivalent; therefore, migration testing for the model 2800 can be applied to the model 2900.

for 20 million cycles to test valve migration up to an equivalent of 6 months of real-time testing. Table 3 describes the pressure conditions during AWT testing. After AWT, the valve-in-valve relative distances were measured again. The initial deployment relative distances were subtracted from the position measured after AWT testing, to determine if the valve had migrated. The results are summarized in Table 3. The migration for the valve-in-valve samples ranged from 0.01 ± 0.27 to 1.61 ± 0.92 mm. Pictures and X-rays were taken of each valve combination after measuring. An example of a valve-in-valve configuration test article is shown in Figs. 2 and 3.

Results for dislodgement pressures, summarized in Table 3, ranged from 400 to >800 mmHg. Due to tester limitations, the highest test pressure that valves were subjected to was 800 mmHg.

Migration measurements taken before and after testing showed that the cloth valve is resistant to significant migration when deployed in the indicated surgical valve.

4. Discussion

Compared with the rigorous ISO 5840:2500 valve standards, the Edwards SAPIEN + cloth THV implanted valve-in-valve within the CEP valve demonstrated excellent hydrodynamic performance. In addition, based on previous testing and valve-in-valve cases being performed with the Edwards SAPIEN implanted into prosthetic Carpentier-Edwards Tissue Valves [1—4] with appropriate model numbers and sizes (per Table 4), the procedure is feasible [5,6].

Acknowledgments

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Appendix A. Conference discussion

Dr G. Bolotin (*Haifa, Israel*): This subject will probably be very important for all of us in the coming years. Valve-in-valve implantation is one of the most appealing indications for this novel technology. The potential advantages are clear: not too much calcium as in the native annulus, and a clear and easy to see old valve ring as a perfect marker for implantation of the new valve-in-valve in the old degenerative biological valve. As mentioned, the potential number of patients is huge due to increasing life expectancy combined with the trend to implant conventional bioprosthetic valves in a younger age population.

In a way, I think that the valve-in-valve option already changes our daily practice. I think that even if the patient is a first time AVR, the potential use in the future of valve-in-valve implantation is a good reason for going down with the age of the first operation.

I have two questions for you. Can you tell us which of the commonly used biological valves and which sizes that we implant today will be suitable for future valve-in-valve implantation and which should we perhaps try to avoid? And the second question. We all already see a growing number of patients with old degenerative valves. Do you think it is already time with the currently available TAVI valves to start valve-in-valve implantation in a wide range?

Dr Walther: Your comments both focus on the use of the SAPIEN in competitor valves in a broader picture. Of course, in this study we could only test valves from Edwards. You saw there were several numbers and they were always very specifically tested over millions of cycles, and this involves quite some work in a pulse duplicator. There were not a sufficient number of competitor valves available for additional testing. Therefore if you conduct a clinical study, it will be difficult to include other competitor valves because the ISO standards haven't been tested. However, off-label implantation has been done in several cases. If you indicate it to your patient, you can do this straight away. There is a nice paper by John Webb with 24 valve-in-valve patients in all four positions, and I may refer to it a bit because I know the data better to our own paper in the Annals early this year with 11 patients valve-in-valve into six different types of xenografts, and we could only give some recommendations based on our experience which valve would fit which valve. However, this testing which was described here is more precise, and this is 100% firm that the valve will now work if it fulfills these 200 million cycles and so on.

In the future it will be important to get the data for valve-in-valve implantation in the clinical scenario, and Dr Eggebrecht, who is an interventional cardiologist at Essen, has collected some data from Germany and will come up with a manuscript on the multicenter results of valve-in-valve, because several centers just have a few, and I suggested to him that he

has a kind of video clip database to see how others implanted those. So if you have a patient, you can contact him and get a video clip and see how others did that or contact some of those who have done some implantations, and, of course, ask for some recommendations regarding the size. But this is not that well tested as the results here with SAPIEN into Edwards valves for sure.

Dr F. Maisano (*Milan, Italy*): Thomas, you have shown us a valve which is not yet available on the market, the SAPIEN with cloth. There are obviously two questions I have regarding this design. One is how much the cloth increases the delivery system size, and, number two, how much the cloth decreases the effective orifice area of the trans-catheter valve?

Dr Walther: Important questions. I am not sure whether it changes the effective orifice area that much and I am pretty sure that you just squeeze it in. You have four atmospheres and really it is just filling little gaps there. We have used that valve in the initial TRAVERSE study in about 10 patients, and we thought that this would be helpful to seal off against paravalvular leak.

The question of when it will be available, I am not so certain. I hope it will come pretty soon. I think it will be an advantage, at least for the trans-apical approach, where tight crimping is not an issue. You need a slightly larger sheath, but you have a valve that could better seal off against irregular calcifications, even primary aortic valve implantations.

Dr M. Romano (*Massy, France*): Why do you recommend oversizing the SAPIEN valve considering that the internal diameter of every bioprosthesis is inferior to that of the sewing ring? So for a 23 mm sewing ring implanted valve where you have an internal diameter of 21, why put a 25?

There was a paper, and I don't remember the name of the authors, in the Journal of Heart Valve Disease last July 2009. They tried to deploy SAPIEN valves in a bioprosthesis and they discovered that the SAPIEN valve does not deploy correctly. Probably it could result in malfunction of the valve, let's say a high gradient, and maybe also early degeneration of the SAPIEN valve. Can you comment on this? And what is the need for an outer skirt that could increase the place required inside the bioprosthesis to place the valve-in-valve?

Dr Walther: Well, the outer skirt is just to seal off against irregularities at the annular level with the pericardial leaflets. I just have to believe what has been done in 200 million cycles in the pulse duplicator to watch some leakage. As to the same question regarding the sizing, there are clear recommendations and I think it is a kind of safety margin for us as clinicians, based on these experimental data, that you should put this or that size inside this or that degenerated Edwards xenograft, if that happens. Of course, you are right, if you do too much crowning, you saw the clinical picture, you may run into problems. Of course, at present we are still limited. There will be a 20 mm valve which would be suitable for some smaller sizes. There may be a 29 at some point, CE approved and available for larger valves and so on. So this is an evolving field. But at present I can just refer to these tests that have been done for specific sizes. You have a very clear number.

The hemodynamics may not get perfect. You can never obtain better hemodynamics than the original xenograft had. So at present I think the indication is still for a high-risk population. If you have a patient who has some patient—prosthesis mismatch, valve-in-valve will not cure that. You can just cure some leaking leaflets or some restenosed leaflets, but you will have the same gradients.

Dr Romano: And this could affect the longevity of the valve?

Dr Walther: Difficult to say. We cannot really tell. The pulse duplicator measurements, of course, fulfill the ISO standards 10, 15 years, for frame and for leaflet durability, and I think this is pretty promising. That is the best standard we can use at present in the lab and we have to see in clinical practice.

Dr Romano: I entirely agree with you.