Transcatheter Aortic Valve Therapies

Insights and Solutions for Clinical Complications and Future Perspectives

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Insights and Solutions for Clinical Complications and Future Perspectives

Percutane aortaklep implantatie

Inzichten en oplossingen voor klinische complicaties en toekomstperspectieven

Proefschrift

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Voor mijn ouders

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Introduction

GENERAL INTRODUCTION

Degenerative aortic stenosis is a progressive disease with a peak in the elderly population (1). One-and-a-half decade ago professor Alain Cribier pioneered a less invasive strategy, with the first in human transcatheter aortic valve implantation (TAVI) (2). TAVI was initially tested and approved in patients who were inoperable or at high risk for death or complications with surgical aortic valve replacement (SAVR) (3-5), but the landscape has changed. While TAVI is maturing, adoption and penetration has expanded to patients at intermediate surgical risk (6-8). Although the concept of TAVI is appealing and intuitively less invasive than SAVR, the procedure still comes with a penalty of complications. Firstly, this thesis summarizes the principle periprocedural complications and evaluates possible solutions in order to push new frontiers in TAVI. Secondly, the focus of this thesis shifts toward expanding the technology to new indications.

The introduction of uniform clinical endpoint definitions has led to a comprehensive overview of TAVI related complications (9). TAVI involves implantation by radial or balloon expansion of a stented frame within the aortic root. The anatomical position of the cardiac conduction system lies in close proximity to the aortic valve. Consequently, radial expansion of a transcatheter heart valve might affect cardiac conduction (10). When this damage is permanent, patients might need a pacemaker. Some patients might be more prone to conduction disturbances and in some instances they might resolve. Part I of this thesis zooms in on this concept.

In contrast to percutaneous coronary intervention, TAVI requires large bore vessel access with an increase in vascular complications such as bleeding, dissection, pseudoaneurysms. Newer device iterations have a smaller profile and thus require through smaller arteriotomies. Percutaneous arteriotomy closure systems are based on sutures. Part II of this thesis will address vascular complications and introduces collagen plug based closure devices for large bore arteriotomies.

Up to 5% of patients experience a clinically significant stroke after the TAVI procedure (11), in particular within the first 48 hours (12). With TAVI, interaction of the delivery system across the aortic arch and within the aortic root may dislodge tissue, which may embolize to the brain, causing ischemic stroke (13). Part III of this thesis discusses cerebral embolization and the value of cerebral embolic protection devices to reduce its incidence.

Multi-modality imaging is essential for procedural planning in terms of transcatheter heart valve design and size selection. The success of TAVI has stimulated product refinement and has brought competitive valve designs and implantation technologies. Part IV of this thesis will touch upon pre-procedural planning and the use of imaging strategies in optimizing the interplay between a transcatheter heart valve and the anatomical landing zone of the patient.

The final chapter of this thesis explores new indications for TAVI. The aortic valve typically contains three leaflets (tricuspid). Aortic stenosis is a degenerative disease characterized by valvular endothelial damage, inflammation and calcification. Aortic valve degeneration develops over many years and typically becomes apparent in the elderly population. In up to 2 to 5% of the population the aortic valve has only 2 leaflets (bicuspid) (14). Bicuspid valves are more prone to degeneration and aortic stenosis thus affects patients at an earlier age (15). The landmark randomized trials on TAVI excluded patients with bicuspid aortic stenosis (3-5). TAVI may be more challenging in bicuspid AS. Finally, even moderate aortic stenosis may be relevant in patients with heart failure and a depressed left ventricular function. The cornerstone

of heart failure therapy is after load reduction with medical therapy (16,17). It is conceivable that moderate aortic stenosis may be detrimental to a failing ventricle. This thesis takes a deeper dive into these 2 entities – severe bicuspid AS and moderate AS with depressed LV function – as interesting targets for TAVI and expanding future indications.

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CHAPTER I

TAVI with current CE-marked devices: strategies for optimal sizing and valve delivery

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ABSTRACT

Transcatheter aortic valve implantation (TAVI) has evolved from an exclusive, highly complex and hazardous procedure into a mature, safe and streamlined therapy for patients with severe aortic stenosis (AS). Various successive device iterations and product refinements have created a dynamic and competitive field with a spectrum of different CE-marked transcatheter heart valve (THV) designs. This review provides a practical overview of current CE-marked THVs with a focus on respective sizing algorithms and delivery strategies.

INTRODUCTION

Transcatheter aortic valve implantation has evolved from an exclusive, highly complex and hazardous procedure into a mature, safe and streamlined therapy for patients with severe aortic stenosis. TAVI uptake and adoption have increased exponentially and the annual TAVI rate has already surpassed SAVR in selected nations (1). More liberal patient selection and the exploration of new indications, such as asymptomatic severe AS, moderate AS with heart failure and aortic regurgitation, may further broaden the TAVI landscape. This remarkable clinical success has stimulated successive device iterations and product refinement, resulting in a dynamic and competitive field with a spectrum of different CE-marked THV designs (2). This review provides a practical overview of current CE-marked THVs with a focus on respective sizing algorithms and delivery strategies.

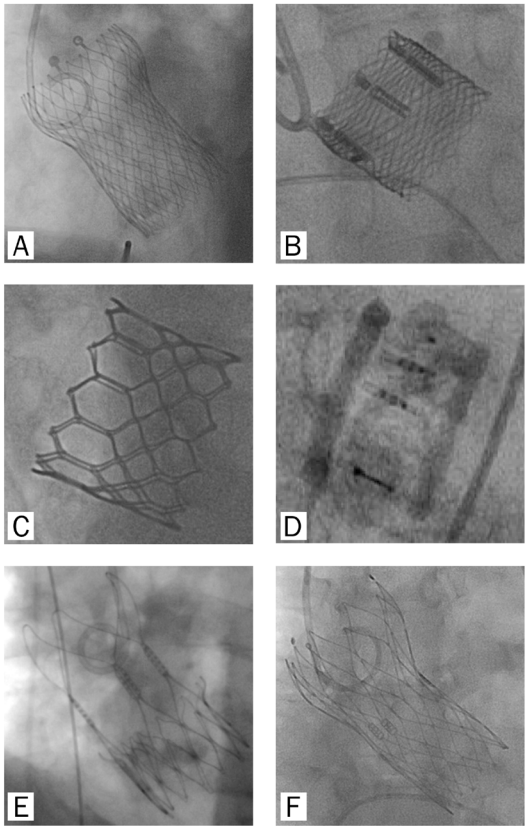

Figure 1. Fluoroscopic views of new-generation transcatheter heartvalves after implantation. A) Medtronic Evolut R. B) Boston Lotus.C) Edwards SAPIEN 3. D) Direct Flow Medical. E) SymetisACURATE. F) St. Jude Portico.

Overview of CE-marked transcatheter heart valves

Medtronic Evolut R

The CoreValve Evolut R device (Medtronic, Minneapolis, MN, USA) consists of a trileaflet porcine pericardial valve housed in a nitinol self-expanding frame and builds on the properties of its CoreValve predecessor (3). A fluoroscopic image of the Evolut R is shown in Figure 1A. The valve leaflets are in a supra-annular position to maximise the effective orifice area and the redesigned nitinol frame has a larger cell size with a smaller frame height of 45 mm. Its inflow has a more consistent radial force to achieve optimal conformation to the aortic annulus. The mid segment is narrower and the outflow segment abuts the aortic wall above the sinotubular junction for improved alignment between valve housing and the native sinus. A 12 mm porcine pericardium fabric skirt surrounds the inflow segment and is continuous with the valve leaflets to protect against paravalvular leakage. The valve is fully repositionable and retrievable up to approximately 80-90% of total deployment. Three valve sizes are currently available covering a range of aortic annular diameters from 18 to 26 mm (Figure 2). The novel EnVeo delivery system and integrated 14 Fr InLine sheath (Medtronic) have significantly reduced the overall profile and are compatible with vessel sizes 5 mm and above. This smaller profile makes a transfemoral approach possible for a wider spectrum of patients, including those with more challenging iliofemoral anatomy including small, tortuous or atherosclerotic vessels.

Boston Lotus

The Lotus valve system (Boston Scientific, Marlborough, MA, USA) is a trileaflet bovine pericardial valve supported on a braided nitinol frame which is deployed through active mechanical expansion, gradually decreasing in size from 70 mm (fully sheathed) to 35 mm upon unsheathing and 19 mm at release (Figure 1B). The nitinol frame expands upon unsheathing and valve function is almost instant. A central radiopaque marker facilitates positioning of the prosthesis within the aortic root. The inflow segment is covered with an adaptive seal to conform to aortic root irregularities and reduce paravalvular leakage. The delivery catheter is attached to the bioprosthesis with three coupling fingers. The valve has a unique locking mechanism that connects the posts to the corresponding buckles and is completely deployed at this point. Valve function and position can be assessed in terms of implantation depth, paravalvular leakage, and location relative to the coronary ostia, and can still be fully repositioned or retrieved when deemed necessary. The Lotus valve comes in three sizes, covering a range of annular diameters from 19 to 27 mm (Figure 2). The delivery system has an 18-20 Fr profile and requires a minimum vessel size of 6 mm.

Edwards Sapien 3

The SAPIEN 3 represents the fourth iteration in the balloon-expandable SAPIEN series (Edwards Lifesciences, Irvine, CA, USA) (4). The cobalt-chromium frame houses three bovine pericardial leaflets and has a polyethylene terephthalate (PET) skirt at its inflow portion and an outer PET sealing cuff to reduce paravalvular leakage (Figure 1C). The novel Commander delivery system consists of an outer deflectable flex catheter and an inner balloon catheter with radiopaque alignment markers. A central radiopaque balloon marker and an additional small wheel for fine alignment of the transcatheter heart valve increase accuracy in positioning. The valve is loaded on the balloon in the abdominal aorta, which helps downsize the overall introduction profile. Furthermore, a dedicated 14 or 16 Fr expandable eSheath temporarily expands as the device passes through the iliofemoral vessels (minimum diameter 5.5 mm) and then recoils to its smaller caliber. There are four available valve sizes to accommodate aortic annular diameters ranging from 18.5 to 29.5 mm (Figure 2).

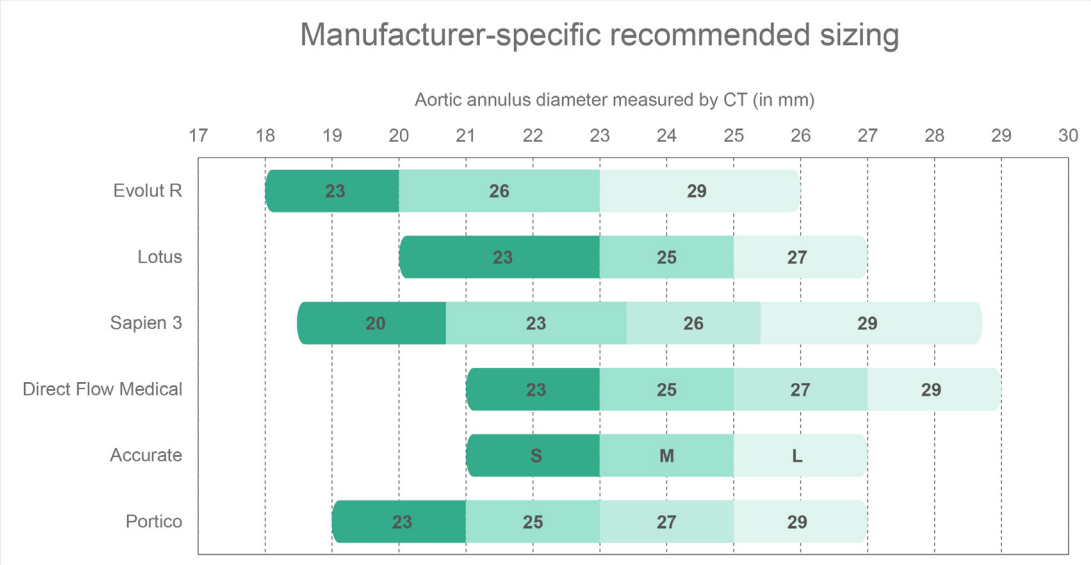

Figure 2. Combined sizing chart of new CE-marked transcatheter heart valves.

Direct Flow Medical

The Direct Flow Medical device (Direct Flow Medical, Santa Rosa, CA, USA) is an 18 Fr compatible trileaflet bovine pericardial valve attached to a non-metallic frame covered by a polyester fabric (Figure 1D) (5). Flexible pillars connect the aortic and ventricular rings which are inflated with a radiopaque solution. The system is unsheathed in the left ventricle followed by inflation of the ventricular ring and retraction of the device into the aortic root. Three positioning wires allow final manipulation before inflation of the aortic ring. The device can be repositioned or retrieved by deflating both rings if device depth, proximity to the coronaries or residual paravalvular leakage are unsatisfactory. Once the correct device position is confirmed, a quick curing polymer is instilled instead of the radiopaque solution to secure permanent implantation and the valve is released by detaching the positioning wires. The Direct Flow Medical valve comes in four sizes, covering annular diameters from 21 to 29 mm (Figure 2).

Symetis Acurate

The ACURATE TA (for transapical) and neo (for transfemoral) valves (Symetis SA, Ecublens, Switzerland) consist of a nitinol self-expanding frame with three stabilisation arches at the distal/aortic edge, an upper and a lower crown (Figure 1E) (6). The lower inflow crown is covered by a polyethylene terephthalate sealing skirt while the upper crown segment provides supra-annular anchoring and houses three pericardial leaflets (ACURATE neo supra-annular; ACURATE TA intra-annular). Transfemoral deployment follows a top-down approach. The upper crown is released first to capture the native leaflets followed by release of the stabilisation arches and unsheathing of the lower crown. There is no need for rapid right ventricular pacing during deployment. During transapical deployment, the stabilisation arches and upper crown are released first before pulling the system down to embrace and compress the native leaflets. The lower crown is then unsheathed and self-detaches from the delivery system. There are three available valve sizes covering annular diameters from 21 to 27 mm (Figure 2), and the delivery system fits within an 18 Fr transfemoral sheath.

St. Jude Portico

The Portico device (St. Jude Medical, St. Paul, MN, USA) is an intra-annular trileaflet bovine pericardial valve housed in a nitinol self-expanding frame with a height of 47 mm (7). The tubular inflow portion (9 mm height) has a porcine pericardial sealing cuff and the outflow segment (38 mm height) consists of large cells extending the frame towards the ascending aorta to provide stability (Figure 1F). The Portico is fully repositionable and resheathable until approximately 85% of deployment. Implantation starts with expansion and sealing of the inflow segment, with the valve functioning early during deployment. There are four available sizes for annular diameters ranging from 19 to 27 mm (Figure 2). The transfemoral delivery system is a flexible 18 Fr (for smaller valve sizes) or 19 Fr catheter (for larger sizes). The valve can be implanted using dedicated sheaths or via a 19 Fr SoloPath sheath (Terumo Europe NV, Leuven, Belgium).

Delivery strategies

The transfemoral route is the access site of first choice for transcatheter aortic valve delivery and has consistently shown the best outcomes, especially compared to the transapical approach (8). The smaller profile of latest-generation devices has increased the proportion of patients who are eligible for femoral access with a minimum required vessel size currently down to 5 mm. Nevertheless, selected patients may fare better with an alternative access route due to excessive calcification, atherosclerotic disease, tortuosity or

insufficient vessel caliber. Various options exist, including transapical, trans-subclavian/axillary, transcarotid, direct aortic and, more recently, transcaval.

Transapical delivery is possible for SAPIEN 3 and ACURATE TA and the self-expanding systems are compatible with trans-subclavian/axillary access. Direct aortic TAVI can be performed with virtually any device platform and the transcarotid route has been successfully applied in selected centers. The transcaval technique is the newest way of bypassing heavily diseased iliac arteries but requires a non-calcified segment of

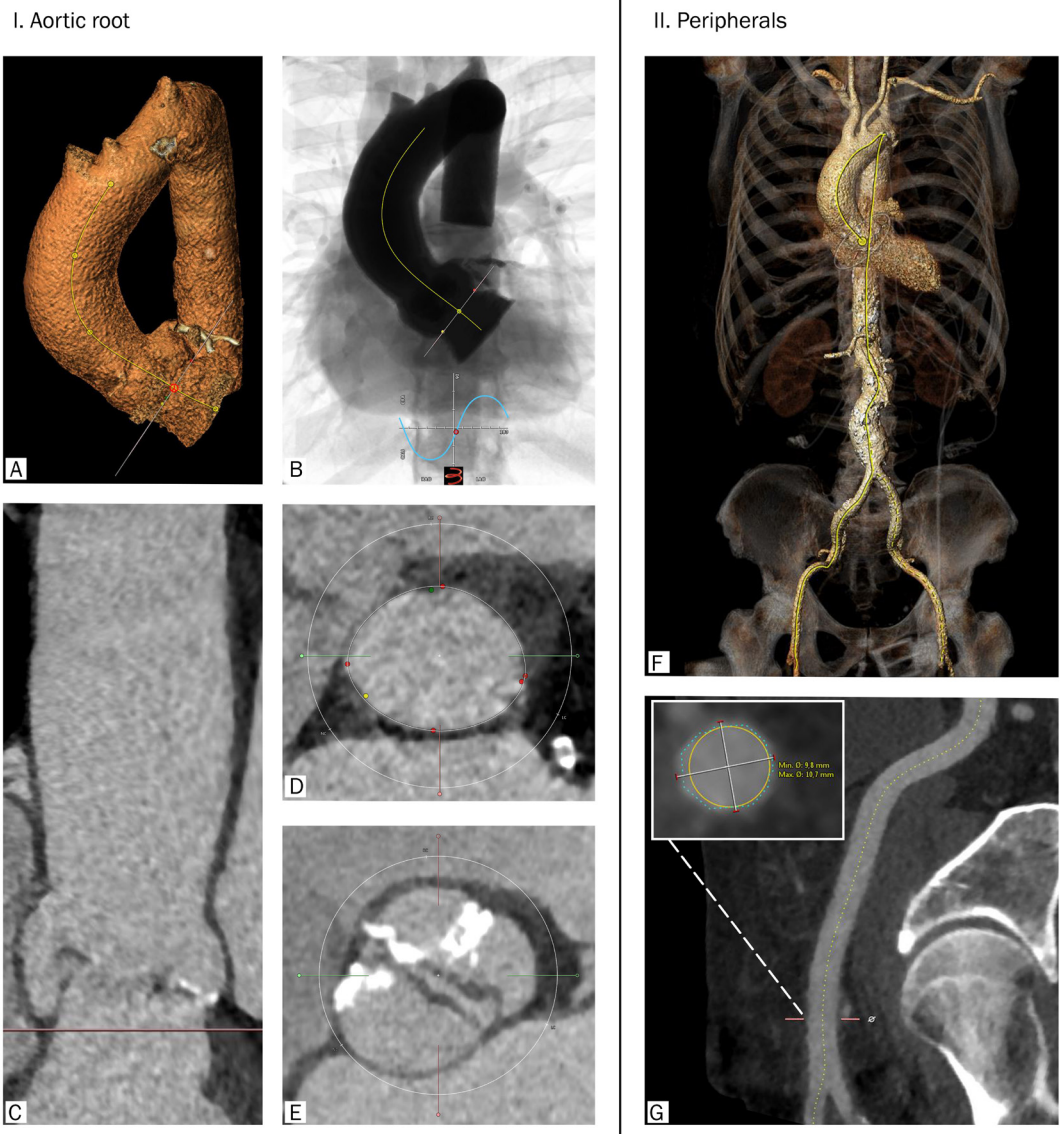

Figure 3. Stepwise analysis of multislice CT with automatic 3mensio software. A) Segmentation and centrelining of aortic root. B) Prediction of optimal C-arm projection. C) Aortic root in a longitudinal view which can be rotated 360 degrees for appreciation of root dimensions and distance to coronaries. D) Smooth tracing of the annular border for calculation of perimeter, area and mean diameters. E) Appreciation of the aortic valve anatomy (in this case a bicuspid aortic valve). F) Three-dimensional reconstruction of peripheral arteries and aorta. G) Estimation of tortuosity and calcium load in the common femoral artery with cross-sectional measurements of vessel diameters at any level.

the abdominal aorta (9). Briefly, the inferior vena cava is connected with the abdominal aorta by puncturing through the venous and arterial walls with a 0.014" "chronic total occlusion" stiff coronary guidewire. Upon entering the aorta, this guidewire is snared and eventually replaced by a stiff 0.035" guidewire. The TAVI procedure is then completed as a typical retrograde transfemoral procedure. After valve delivery, the aorto-caval communication is typically closed with St. Jude AMPLATZER™ nitinol closure devices (VSD or PDA occluders). The fate and adoption of alternative access strategies remains unclear. Indeed, relatively straightforward execution without the need for general anesthesia is arguably the most attractive feature of the standard retrograde transfemoral approach. Multislice computed tomography (MSCT) angiography is currently the preferred imaging tool for comprehensive assessment of the entire arterial tree relevant to TAVI. Conventional angiography may provide additional information given its superior spatial resolution or when CT imaging is suboptimal. A major limitation of ultrasound examination is its inability to visualise the retroperitoneal space.

Valve size selection

Pre-procedural imaging planning is key for any successful TAVI programme. Access site, transcatheter heart valve and consequent device sizing typically rely on MSCT (Figure 3). Inaccurate sizing may have important clinical consequences. Undersizing can result in prosthesis-patient mismatch, paravalvular leakage, device migration and embolisation, all of which can adversely influence prognosis after TAVI. Conversely, oversizing may lead to annular rupture, prosthesis underexpansion with subsequent risk of central transvalvular regurgitation, and conduction abnormalities due to excessive compression of the conduction system in the LVOT. An integrated sizing chart for current CE-marked THVs is displayed in Figure 2. Of note, self-expanding devices typically require more oversizing relative to the native anatomy, as opposed to closer matching with the SAPIEN 3, Direct Flow and Lotus devices. Several imaging modalities are available to measure native annular dimensions and help guide THV size selection.

Multislice computed tomography (MSCT)

A single MSCT study can offer vital information concerning the aortic root and entire relevant arterial trajectory, including the aorta, subclavian and iliofemoral system. MSCT has become the standard for 3D assessment of the aortic root in terms of dimensions, calcium distribution and height of the coronary ostia relative to the virtual annulus (10). Various dedicated software packages (3mensio (Pie Medical Imaging, Maastricht, The Netherlands), Philips Heart Navigator (Philips Medical Systems, Eindhoven, The Netherlands), Siemens syngo Aortic Valve Guide (Siemens AG, Munich, Germany) and GE Innova (GE Healthcare Ltd, Little Chalfont, Buckinghamshire, UK)) simplify the process of multiplanar reconstruction and make these advanced analyses accessible to interventionalists without extensive radiological training. Interestingly, sizing charts for self-expanding systems rely on aortic annular perimeter (and derived diameters) whereas area is the preferred parameter for balloon and mechanically expandable THVs. Derived diameters will not differ much in principle although the perimeter is less influenced by anatomic variation during the cardiac cycle and may result in larger derived diameters.

Echocardiography

Transthoracic echocardiography is not as accurate as transoesophageal echocardiography and 2D echocardiography requires expert interpretation to ensure that the aortic annulus is viewed in the correct plane to avoid underestimation of minimum and maximum diameters. The advent of 3D echocardiography may fix this important limitation, although the spatial resolution of 3D TOE remains inferior to MSCT and aortic calcification may negatively affect imaging quality. Controversy surrounds the correlation between 3D TOE and MSCT sizing. Importantly, TOE quality depends on the experience of the echocardiographer and is characterized by wider inter-observer variability. In a recent study, aortic annulus measurements were significantly smaller with TOE versus MSCT, particularly in more oval annular anatomy (11). Three-dimensional TOE is a valid alternative to MSCT in patients with severe renal insufficiency (to avoid contrast exposure) or a suboptimal MSCT study (e.g., motion artefacts, out-of-phase contrast injection).

Magnetic resonance imaging

Cardiac magnetic resonance imaging (CMR) is a valid alternative to MSCT for device sizing. CMR is effective to determine aortic root dimensions and evaluate thoracic arterial structures yet struggles with calcium and cannot be used in patients who have an MRI non-compatible pacing device or are claustrophobic.

Other modalities

Rotational angiography (R-angio) is a novel technique performed in the catheterisation laboratory using simultaneous C-arm rotation and diluted contrast injection. R-angio provides CT-like reconstruction of the aortic root with accurate sizing; however, patient characteristics (e.g., BMI >29 kg/m²) and a significant learning curve hamper its adoption in clinical practice (12).

Simultaneous balloon aortic valvuloplasty and supra-aortic contrast angiography may help in root sizing and demonstrate the interaction of native aortic valve leaflets with the coronary ostia. This ancillary technique may be particularly helpful when MSCT sizing is ambiguous between two consecutive device sizes (13,14).

CONCLUSION

Multiple CE-marked options for TAVI exist and MSCT is now the cornerstone to determine the optimal selection of the appropriate access site, transcatheter valve design and size.

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CHAPTER II

Boston Lotus

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Percutaneous Treatment of Left Side Cardiac Valves. A Practical Guide for the interventional Cardiologist.
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DESCRIPTION OF THE VALVE AND DELIVERY SYSTEM

The Lotus valve system (Boston Scientific, Marlborough, MA, USA) consists of a trileaflet bovine pericardial valve supported on a braided nitinol frame (Figure 1). A central radiopaque marker facilitates positioning of the prosthesis within the aortic root. The frame is covered with an Adaptive Seal at the inflow segment that adapts to aortic root irregularities and minimizes paravalvular leak (Figure 2).

Figure 1. The Lotus Valve.

This transcatheter heart valve is currently available in three sizes - 23, 25, and 27 mm (Figure 3) - covering a range of annulus diameters from 19 to 27 mm. In fully deployed state, all sizes have a frame height of 19 mm. The 23 mm model can be delivered through an 18 Fr sheath (small), while the 25 and 27 mm valves require a 20 Fr (large) sheath.

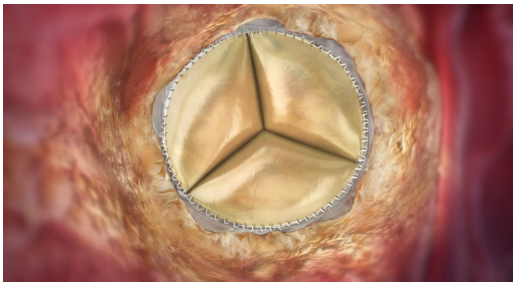

Figure 2. The Adaptive Seal technology covers the inflow segment of the Lotus valve frame and adapts to aortic root irregularities and, hence, minimizes paravalvular leak.

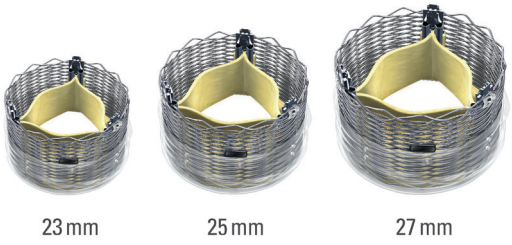

Figure 3. The three available Lotus valve sizes —23, 25, and 27 mm— accommodating annulus diameters ranging from 20 to 27 mm.

Lotus is typically inserted with a transfemoral approach, though direct aortic and transaxillary alternative access is possible. Implantation of a Lotus valve requires the following components:
– A support guidewire: either a manually curved Super/Extra Stiff 0.035" guidewire (260 cm for 23 mm and 275 for 25 and 27 mm) or a pre-shaped Safari guidewire with an extra-small, small, or large curve (Figure 4).

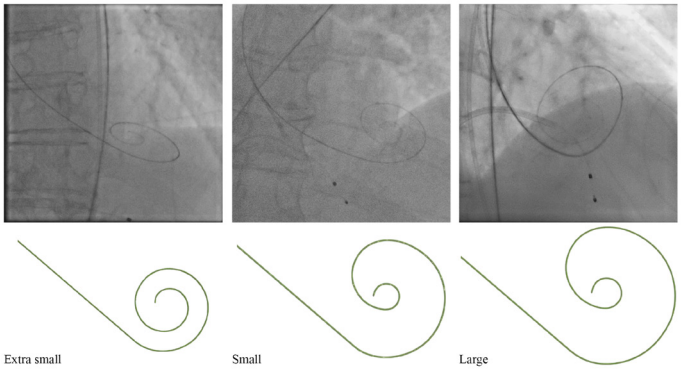

Figure 4. The pre-curved Safari wire comes in three curve sizes to facilitate stability for valve implantation in small and large ventricles.

– Lotus introducer—small for 23 mm and large for 25 and 27 mm (Figure 5).
– Lotus valve delivery system, with pre-mounted Lotus valve —103 cm for 23 and 113 cm for 25 and 27 mm (Figure 6). The pre-shaped angulated delivery system should help negotiate the thoracic aorta.
- Prostar or double Perclose ProGlide (Abbott Vascular, Abbot Park, Illinois, USA) suture-based closure for transfemoral access (Figure 7).

Figure 6. Lotus delivery system. Top, the pre-mounted Lotus valve; bottom, the intuitive delivery handle with the blue control knob for unsheathing/re-sheathing and locking and the black release cover for release of the valve.

Figure 5. Lotus introducer (small). The light blue 18 Fr Lotus introducer accommodates transfemoral access for the small Lotus delivery system (23 mm valve).

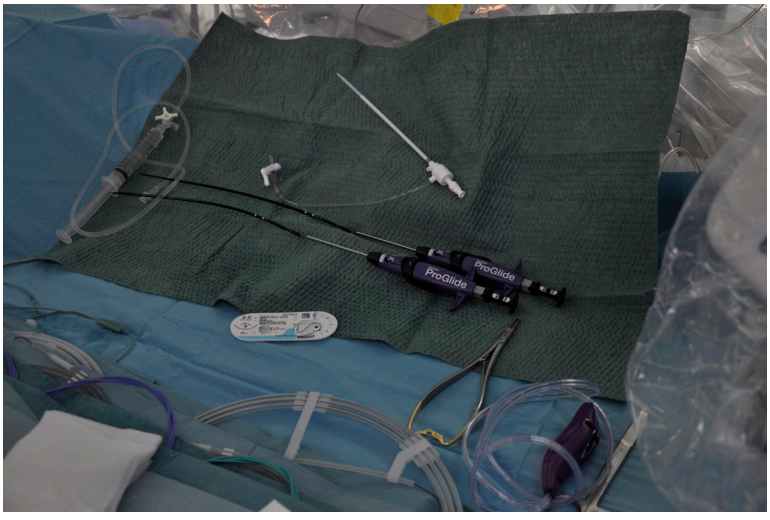

Figure 7. Double Perclose ProGlide systems. ProGlide provides percutaneous suture-based closure of femoral access arteriotomies, ranging from 5 Fr to 21 Fr.

Figure 8. Three fingers connect the Lotus valve to the delivery system throughout the entire implantation process. The fingers are attached to the buckles on the frame and can be released when the result after complete locking is satisfactory.

The bioprosthesis is coupled to the delivery system with three coupling fingers (Figure 8). The three fingers hatch with the buckles at the top of the frame. Initially the frame expands during unsheathing. The unique feature of Lotus is the locking mechanism that follows after the frame is fully unsheathed but still elongated. The locking mechanism implies connecting the buckles (top of the frame) with the posts (level of valve leaflets), similar to fastening a seatbelt.

The valve shortens and expands radially during the locking process (Figure 9). After locking, the valve is fully deployed, and its position relative to the coronary ostia and presence of paravalvular aortic regurgitation can be assessed. Still, at this stage, the bioprosthesis can be repositioned or retrieved.

The delivery handle of the delivery system is ergonomic and intuitive (Figure 6). A large blue control knob regulates unsheathing and locking by rotating counterclockwise. Clockwise rotation will lead to re-sheathing. The release cover proximal to the blue control knob can be slid forward to release the valve from the catheter.

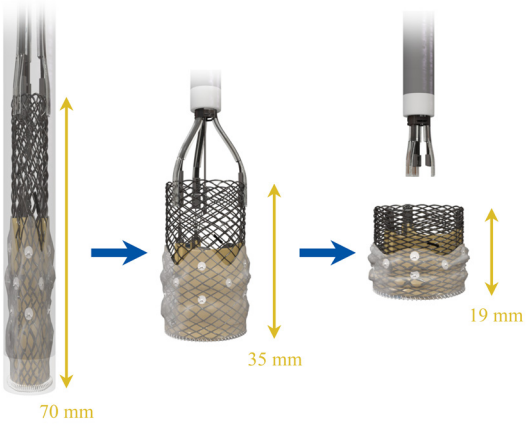

Figure 9. When fully sheathed, the Lotus valve frame has a height of 70 mm. During unsheathing the height of the valve frame shrinks to 35 mm, while the diameter of the valve increases. During the locking process, the frame shrinks to a height of 19 mm and reaches its final configuration with maximal sealing of the annulus.

Figure 10. The pre-mounted Lotus valve is conserved in a bottle stopcock containing glutaraldehyde.

Figure 11. Before delivery, the valve is visually screened for abnormalities by checking the catheter tip and finger connection, collar and buckle interaction, sheathing aids, nosecone, and valve leaflets, followed by flushing of the system.

PROSTHESIS LOADING

The loading procedure for the 23, 25, and 27 mm valves is identical. When removed from the package, the valve is sealed within a bottle stopcock at the distal end of the delivery system. The stopcock contains glutaraldehyde for valve conservation:

1. Remove the Luer cap from the bottle stopcock, and attach it to the waste bag to drain the glutaraldehyde solution.
2. Flush the guidewire port at the distal end of the delivery system.
3. Remove the valve from the stopcock (Figure 10).
4. Visually inspect the valve for abnormalities (catheter tip and finger connection, collar and buckle interaction, sheathing aids, nosecone, valve leaflets), and flush the system (Figure 11).

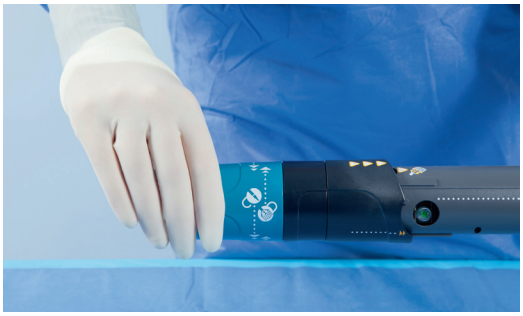

Figure 12. The blue control knob on the delivery handle facilitates unsheathing/locking of the Lotus valve (rotating counterclockwise) and re-sheathing (rotating clockwise). This mechanism is checked before valve delivery.

5. Lock the valve by turning the blue control knob counterclockwise, to ensure post and buckles engage without a gap and there is no twisting (Figure 12).
6. Turn the blue control knob clockwise to ensure post and buckles disengage symmetrically.
7. Rinse the valve with agitation 2 × 60 s.
8. Insert a stylet in the nosecone and flush the system with saline.
9. Remove air bubbles from the leaflets by agitating the valve.
10. Submerge the valve in saline, and wait until the valve can be delivered.
11. Once the valve can be delivered, gently start sheathing the valve by turning the blue control knob clockwise.
12. Remove the stylet and inspect the catheter tip. The delivery system is ready.

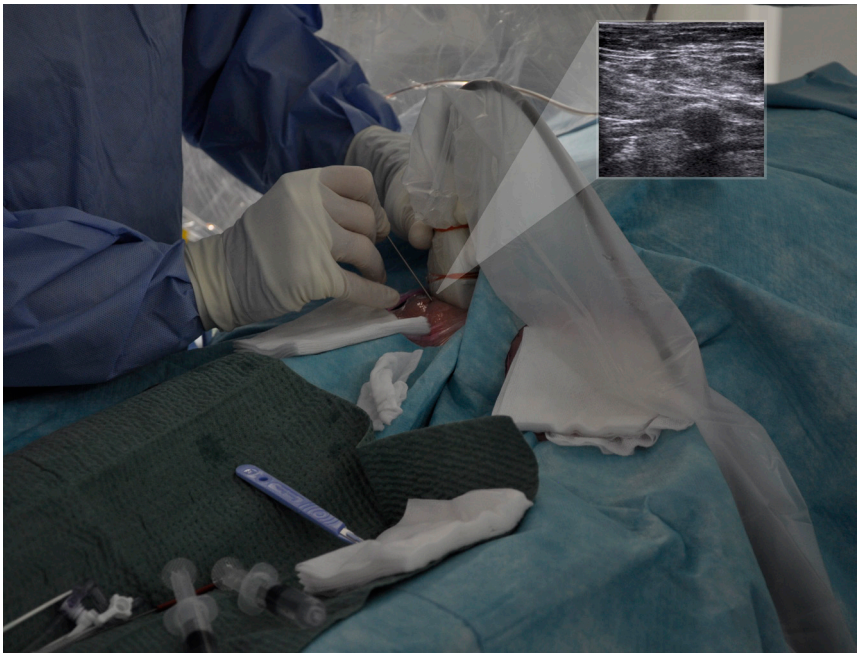

Figure 13. Echo-guided puncture of the right common femoral artery. On an axial plane the location of the vessel can be accurately determined.

TYPICAL TRANSFEMORAL IMPLANTATION PROCEDURE

Obtaining Vascular Access

1. Obtain controlled access to the left and right common femoral arteries, preferably under fluoroscopy or ultrasound guidance (Figure 13).
2. Obtain venous access for a temporary right ventricular pacing wire.
3. Position the temporary pacing wire in the apex of the right ventricle, and test the pacemaker.
4. Insert a pigtail catheter through the left femoral artery, and position at the level of the non-coronary cusp; confirm a coaxial C-arm projection with a contrast injection to have all cusps in one plane (Figure 14).

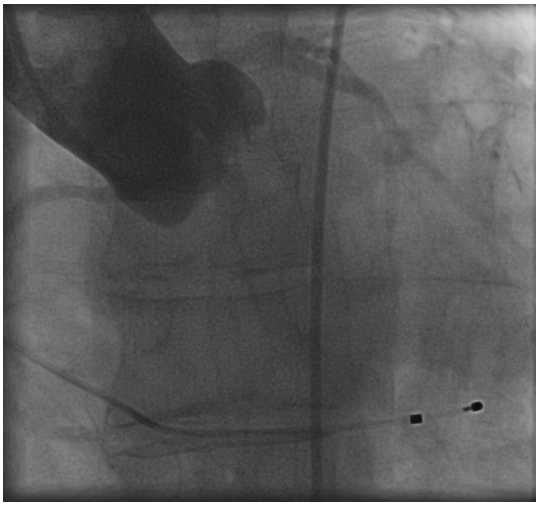

Figure 14. Angiogram of the aortic valve in a perpendicular plane with all cusps aligned (NCC-RCCLCC). An optimal working projection contributes to an accurate valve implantation.

5. Preclosure with two 6 F Perclose ProGlide systems (or 1 Prostar) in the right femoral artery.
6. Insert the 18 F introducer (small) or 20 F (large), depending on the bioprosthesis size (Figure 5).
7. Cross the aortic valve with a 0.035 straight tip wire, and advance a catheter in the left ventricle.
8. Confirm ventricular pressures and transaortic gradient.
9. Exchange for a Safari wire (Figures 4 and 15). Ensure the pre-shaped curve of the Safari wire is positioned in the apex, and the soft part of the wire is entirely curled in the ventricle. This will provide enough safe migration space for the nosecone (see below).
10. Decide whether to perform balloon predilatation. In our practice, balloon predilatation is performed only exceptionally.

Valve Delivery

1. Hold the pre-shaped delivery system in an S-curve, and insert over the Safari wire into the body (Figure 16a).
2. Advance the assembly gently, under fluoroscopic guidance, keeping guidewire control and checking proper orientation along the descending aorta (Figure 16b). The radiopaque marker should be facing the right side of the delivery system on an AP fluoroscopic view before entering the aortic arch (Figure 17).

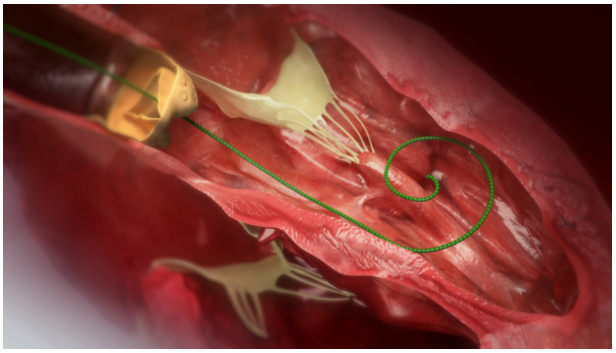

Figure 15. Animation of a Safari wire positioned in the left ventricle.

3. Smoothly advance the system along the aortic arch (Figures 16b and 17).
4. Cross the native aortic valve and ensure the nitinol braid is below the aortic annulus (Figure 18a1).
5. Determine the final landing zone of the radiopaque marker.
6. Start unsheathing the valve by turning the blue control knob counterclockwise (Figures 16c and 18A2/A3/A4).

7. Avoid excessive device migration into the left ventricle. The Lotus valve functions early during deployment; there should be no hemodynamic compromise.
8. As the valve deployment evolves, a waist will appear, and the radiopaque marker is displaced toward the ventricle.
9. The framework shortens from 70 to 35 mm upon unsheathing.

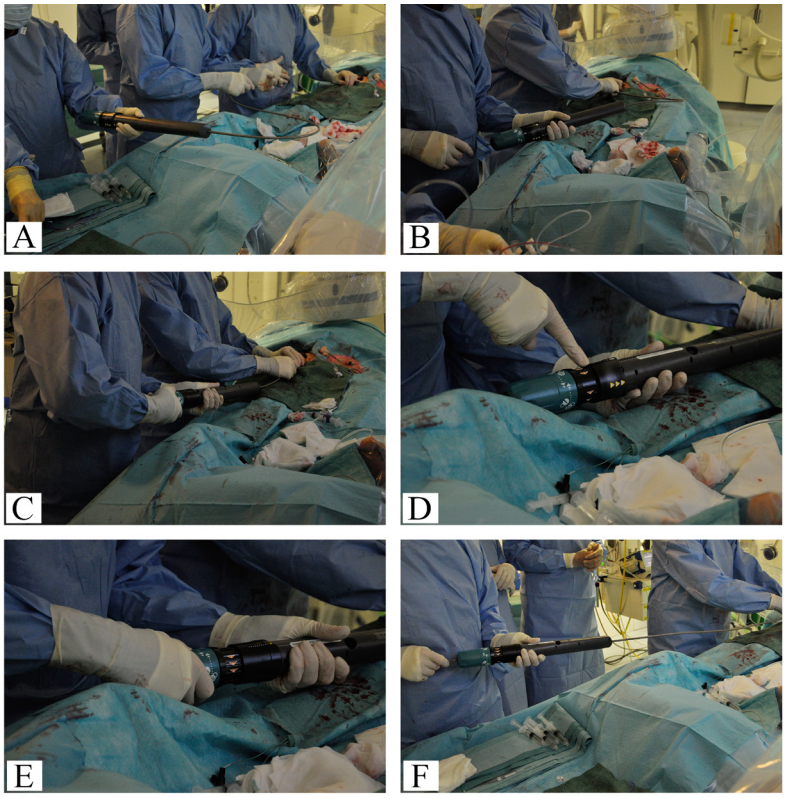

Figure 16. Stepwise Lotus valve implantation: (a) delivery system is held in the pre-shaped S-curve before introduction; (b) delivery system is smoothly advanced by pushing forward through the Lotus introducer; (c) when the tip of the delivery system is in the correct position (with the nitinol braid below the native annulus), the valve can be unsheathed and locked by turning the blue knob counterclockwise; (d) release cover is slid toward the patient and turned clockwise to release the valve; (e) blue control knob is turned counterclockwise to re-sheath the disconnected fingers and nosecone; (f) delivery system is pulled back gently through the introducer.

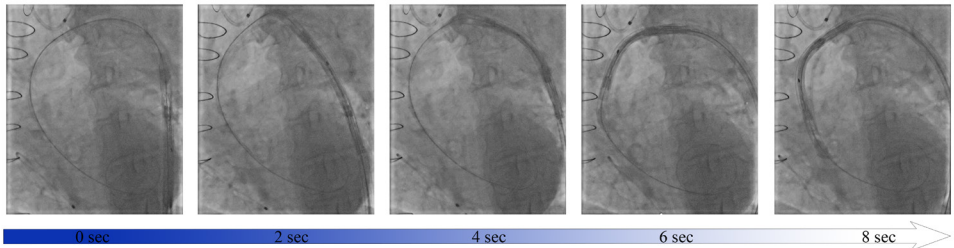

Figure 17. During crossing of the aortic arch (in approximately 8 s), the delivery system is carefully monitored to ensure that the radiopaque marker follows the outer curve of the arch.

Locking

The next step is locking the valve by connecting the buckles (cranial) and posts (caudal).

1. Before initiating the final locking process, confirm that the fluoroscopy projections show all three buckles and posts (Figure 18B1).
2. Gently turn the blue control knob counterclockwise while confirming that the buckles and posts approach symmetrically. During this process, the frame height will shrink from 35 to 19 mm (Figure 18B2).
3. The valve is completely locked, resistance is felt, and a force limiter is tripped. An audible sound is heard.

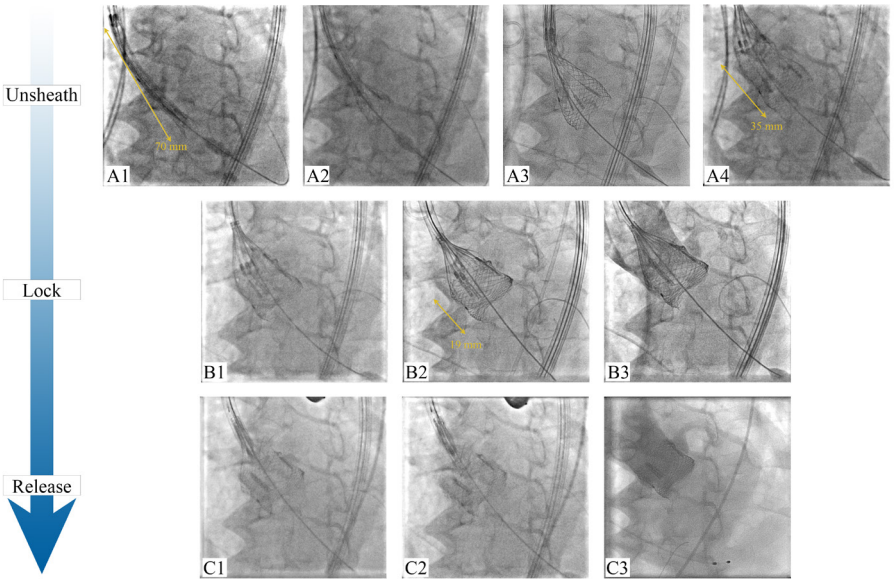

Figure 18. Unsheathing: (a1) fully sheathed Lotus valve (frame height 70 mm) with the distal tip of the nitinol frame below the native annulus; (a2/3) unsheathing of the valve. The valve functions early during deployment; (a4) fully unsheathed valve (frame height 35 mm). Locking: (b1) locking of the frame in a correct fluoroscopic image with all buckles and posts visible; (b2) fully locked frame (frame height shrinks to 19 mm); (b3) angiogram to confirm correct positioning after locking and absence of significant paravalvular regurgitation. At this stage, the valve is still fully repositionable and re-sheathable. Release: (c1/2) disconnecting the fingers from the frame buckles; (c3) final angiogram to evaluate position and paravalvular regurgitation.

4. Final valve positioning relies on the confirmation that the distal braid is below the annulus (this may allow for a high position) or by landing the radiopaque marker at its predetermined location.
5. After locking the valve, a contrast injection may help confirm valve positioning in terms of implantation depth, position relative to the coronary ostia, and paravalvular regurgitation (Figures 19 and 18B3).

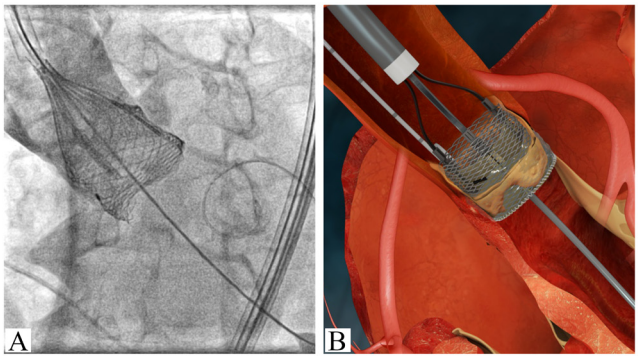

Figure 19. Fully locked Lotus valve before release on fluoroscopy (a) and reconstructed (b). The valve can be repositioned at this stage.

Release

1. Slide the release cover (located distal to the blue knob) in the direction of the patient (Figure 16D).
2. Turn the release cover clockwise. The release pin moves upward. The valve is released (Figure 18C1/2).
3. When the valve is completely released, start re-sheathing the fingers and nosecone by turning the blue control knob clockwise. Gently pull the nosecone back into the descending aorta and fully re-sheath.
4. The final position of the Lotus valve can be properly visualized by transthoracic or transesophageal echocardiography (Figure 20) and on fluoroscopy (Figure 21).

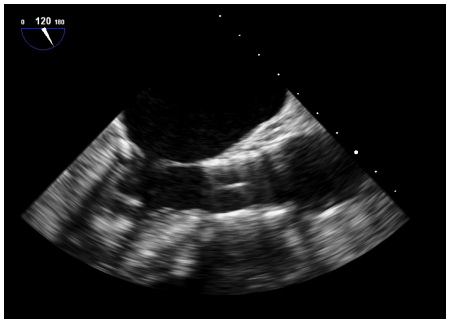

Figure 20. Long-axis transesophageal echocardiographic view of the Lotus valve after final release.

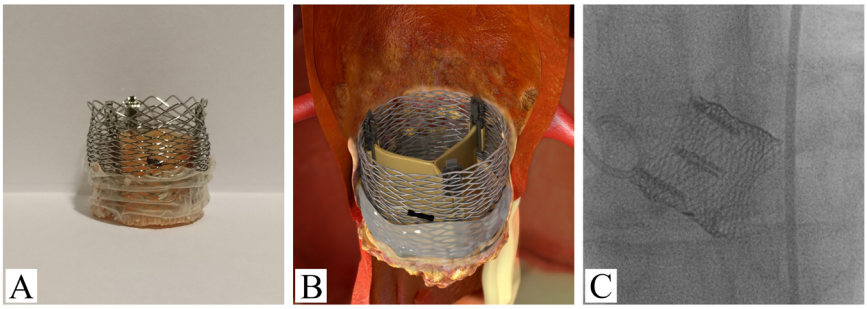

Figure 21. The Lotus valve after final locking and release: (a) lotus valve with central radiopaque marker and Adaptive Seal; (b) reconstruction of a Lotus valve in the correct anatomical position; (c) fluoroscopic image of the Lotus valve.

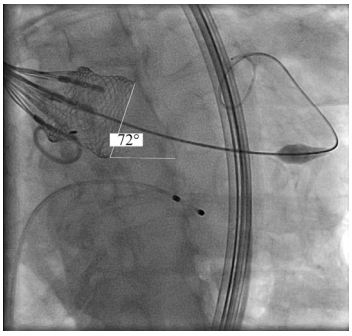

Figure 22. Fluoroscopic image of a fully locked Lotus valve in an extremely horizontal aorta with an angle of 72°.

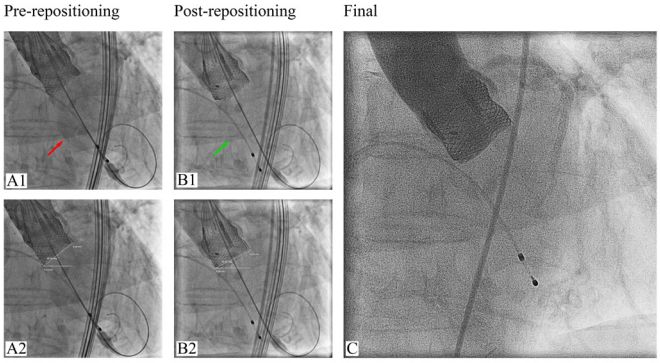

Figure 23. Repositioning of the Lotus valve on fluoroscopy: (a1) aortic angiogram pre-repositioning,moderate paravalvular aortic regurgitation; (b1) aortic angiogram post-repositioning, no aortic regurgitation. (a2/b2) Angle and depth measurements before and after implantation confirming a slight tilting of the frame between pre- and post-repositioning, with a similar depth of implantation; (c) final aortic angiogram with no aortic regurgitation.

Repositioning

The repositionability/retrievability feature allows for precise valve delivery even in complex anatomies (e.g., horizontal aorta (Figure 22)) and readjustment when paravalvular regurgitation is present (Figures 23 and 24). The Lotus bioprosthesis is fully repositionable and retrievable until the valve is fully locked and the release pin is removed. Re-sheathing is done by turning the blue control knob clockwise.

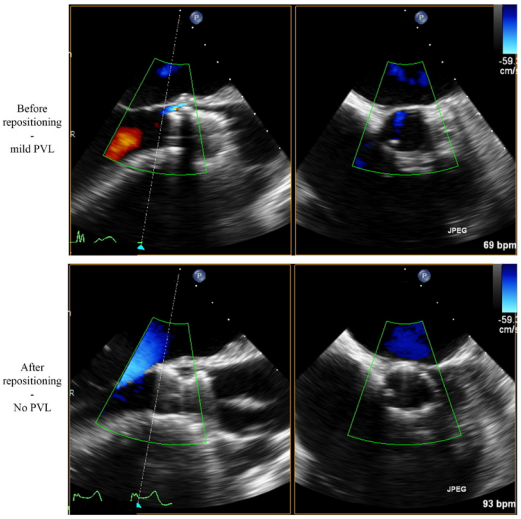

Figure 24. Repositioning of the Lotus valve on transesophageal echocardiography: there was a mild paravalvular leak (at 11 o'clock on short axis), which was resolved after repositioning.

PROCEDURE AND SIZING TIPS AND TRICKS

The Lotus delivery system requires a minimum arterial vessel diameter of 6 mm. The Lotus valve can be implanted in a wide range of native valve diameters (19–27 mm). Figure 25 illustrates the sizing matrix. The 23 mm Lotus fits annulus and LVOT diameters ranging from 20 to 23 mm, the 25 mm Lotus from 23 to 25 mm, and the 27 mm Lotus from 25 to 27 mm. The Adaptive Seal of the Lotus valve can help eliminate the incidence of paravalvular regurgitation. In our opinion, the left ventricular outflow tract dimensions are equally important for Lotus sizing. Excessive oversizing relative to the LVOT and overall depth of implantation may affect the occurrence of conduction disorders and need for pacemakers. It is important to bear in mind that the bioprosthesis will dominate the anatomy, suggesting a more circular final geometry. Coronary obstructions can be avoided by pre-procedure MSCT planning and by checking the Lotus position before release. The bioprosthesis can be repositioned when needed.

Lotus™ Valve System

Sizing Guidelines

CT Measurements for Patient Screening		23 mm	25 mm	27 mm
Actual Lotus Valve	Diameter (mm)	23	25	27
	Perimeter (mm)	72.3	78.5	84.8
	Area (mm²)	415.5	490.9	572.6
Annulus	Diameter (mm)	20 ≤ ideal ≤ 23	23 ≤ ideal ≤ 25	25 ≤ ideal ≤ 27
	Perimeter (mm)	62.8 ≤ ideal ≤ 72.3	72.3 ≤ ideal ≤ 78.5	78.5 ≤ ideal ≤ 84.8
	Area (mm²)	314 ≤ ideal ≤ 415.5	415.5 ≤ ideal ≤ 490.9	490.9 ≤ ideal ≤ 572.6
LVOT[1]	Diameter (mm)	20 ≤ ideal ≤ 23	23 ≤ ideal ≤ 25	25 ≤ ideal ≤ 27
	Perimeter (mm)	62.8 ≤ ideal ≤ 72.3	72.3 ≤ ideal ≤ 78.5	78.5 ≤ ideal ≤ 84.8
	Area (mm²)	314 ≤ ideal ≤ 415.5	415.5 ≤ ideal ≤ 490.9	490.9 ≤ ideal ≤ 572.6
	Unsuitable area (mm²)	< 280	< 330	< 390
SOV[2]	Area too small (mm²)	< 540	< 595	< 650
	Ideal Area (mm²)	> 600	> 700	> 800
	Area too large (mm²)	> 1100	> 1200	> 1300
Annulus to Coronary Height	Height (mm)	Caution if < 10 mm; need to also consider sinus area		
Choosing Between the Margin of the Valve Sizes	Annulus	SMALLER ... LARGER		
	LVOT			
	SOV			
	Burden of Calcium	MORE CALCIUM ... LESS CALCIUM		

Figure 25. Lotus valve sizing guidelines.

Part I
Conduction disorders

CHAPTER III

Transcatheter heart valve selection and permanent pacemaker implantation in patients with pre-existent right bundle branch block

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ABSTRACT

Background

Right bundle branch block is an established predictor for new conduction disturbances and need for a permanent pacemaker (PPM) after transcatheter aortic valve replacement. The aim of the study was to evaluate the absolute rates of transcatheter aortic valve replacement related PPM implantations in patients with pre-existent right bundle branch block and categorize for different transcatheter heart valves.

Methods and Results

We pooled data on 306 transcatheter aortic valve replacement patients from 4 high-volume centers in Europe and selected those with right bundle branch block at baseline without a previously implanted PPM. Logistic regression was used to evaluate whether PPM rate differed among transcatheter heart valves after adjustment for confounders. Mean age was 83±7 years and 63% were male. Median Society of Thoracic Surgeons score was 6.3 (interquartile range, 4.1–10.2). The following transcatheter valve designs were used: Medtronic CoreValve (n=130; Medtronic, Minneapolis, MN); Edwards Sapien XT (ES-XT; n=124) and Edwards Sapien 3 (ES-3; n=32; Edwards Lifesciences, Irvine, CA); and Boston Scientific Lotus (n=20; Boston Scientific Corporation, Marlborough, MA). Overall permanent pacemaker implantation rate post-transcatheter aortic valve replacement was 41%, and per valve design: 75% with Lotus, 46% with CoreValve, 32% with ES-XT, and 34% with ES-3. The indication for PPM implantation was total atrioventricular block in 98% of the cases. Lotus was associated with a higher PPM rate than all other valves. PPM rate did not differ between ES-XT and ES-3. Ventricular paced rhythm at 30-day and 1-year follow-up was present in 81% at 89%, respectively.

Conclusions

Right bundle branch block at baseline is associated with a high incidence of PPM implantation for all transcatheter heart valves. PPM rate was highest for Lotus and lowest for ES-XT and ES-3. Pacemaker dependency remained high during followup.

INTRODUCTION

Patients with severe aortic stenosis and a higher operative risk for mortality are good candidates for transcatheter aortic valve replacement (TAVR) (1-4). TAVR involves placement of a transcatheter heart valve (THV) that protrudes into the left ventricular outflow tract. As such, the THV radial force may impose on the adjacent conduction system and result in conduction disturbances (5,6). Incidence of new left bundle branch block (LBBB) and high-grade atrioventricular block (AV block) varies according to patient demographics, anatomical characteristics, and selected THV. New LBBB and permanent pacemaker (PPM) implantation post-TAVR varies from 4% to 81% and from 0% to 49%, respectively, and is consistently higher with the self-expanding CoreValve compared to balloon-expandable Sapien valves (5,7,8).

New THV designs have focused on profile refinement, paravalvular leak prevention, and the intrinsic feature of partial or complete repositionability and retrievability (9-11), yet conduction disorders remain common. Right bundle branch block (RBBB) at baseline is considered a dominant predictor for high degree AV block and PPM post-TAVR (7,12-16). Frequency of RBBB at baseline in current TAVR practice ranges from 4% to 21% (7). Knowledge of the respective PPM rates for different THV designs in patients with RBBB may guide patient-tailored THV selection. This multicenter collaboration sought to further elucidate TAVR-related PPM rates in patients with pre-existent RBBB and categorize for different THV designs.

METHODS

Patient Selection

Between May 2008 and February 2016, 2845 patients underwent TAVR in 4 tertiary care European institutions. All patients were screened for RBBB (and absence of a PPM) before the TAVR procedure and were included in a joint database collecting: baseline demographics; TAVR procedure characteristics; new conduction disorders within 24 hours; PPM at 30 days; and electrocardiographic and clinical-follow-up data at 30 days and 1 year. THV selection was per institution's discretion. A minimum of 10 available cases per THV was a predefined requirement for further analysis, to secure solidity of data. The 4 THVs used were CoreValve (Medtronic, Minneapolis, MN), Sapien XT (ES-XT) and Sapien 3 (ES-3; Edwards Lifesciences, Irvine, CA), and Lotus (Boston Scientific Corporation, Marlborough, MA). Figure 1 displays the patient flow diagram. All patients provided written informed consent for the procedure and data analysis for research purposes per institutional review board approval.

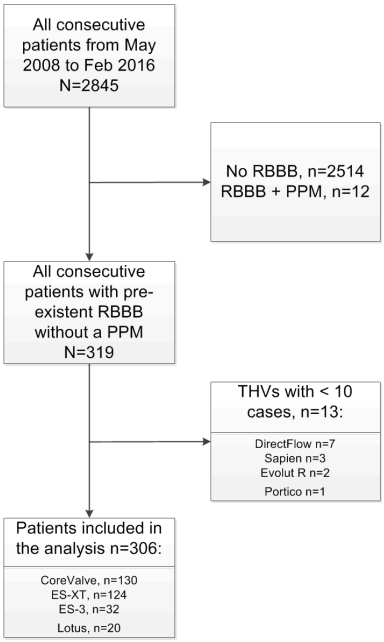

Figure 1. Flow chart of study inclusion. Abbreviations: ES-3 = Edwards Sapien 3; ES-XT = Edwards Sapien XT; PPM = permanent pacemaker; RBBB= right bundle branch block; THVs = transcatheter heart valves.

Outcomes

The primary outcome was implantation of a PPM within 30 days after the TAVR procedure. Secondary outcomes were new-onset conduction disturbances within 24 hours: (1) third-degree atrioventricular block (AV3B) and (2) alternating bundle branch block (i.e. change from RBBB to LBBB). The decision for PPM was per treating physician's discretion, but, in general, in compliance with contemporary European Society of Cardiology Guidelines on PPM (17). Clinical outcomes were reported using the revised Valve Academic Research Consortium criteria (18).

Statistical Analysis

Continuous variables are presented as mean ± SD or median (interquartile range; IQR). Distribution of continuous variables was assessed for normality with histograms and the Shapiro–Wilk test. Continuous variables were compared using a Student t test or Mann–Whitney U test, when applicable. Categorical

	CoreValve (N=130)	ES-XT (N=124)	Lotus (N=20)	ES-3 (N=32)	Overall (N=306)	P-value
Age. mean ± SD	83 ± 6	83 ± 8	83 ± 6	81 ± 6	83 ± 7	0.301
Male sex. n (%)	79 (61)	83 (67)	12 (60)	20 (63)	194 (63)	0.761
BMI in kg/m2. mean ± SD	26 ± 5	27 ± 4	29 ± 7	27 ± 4	27 ± 5	0.319
Diabetes Mellitus. n (%)	33 (25)	38 (31)	9 (45)	13 (41)	93 (30)	0.161
STS-score in %. median [IQR]	6.5 [4.5-10.4]	7.0 [4.0-10.1]	5.9 [5.2-7.8]	4.5 [3.0-10.5]	6.3 [4.1-10.2]	0.186
PVD. n (%)	28 (22)	36 (29)	6 (30)	7 (22)	77 (22)	0.526
COPD. n (%)	41 (32)	40 (33)	5 (25)	7 (22)	93 (30)	0.634
Atrial fibrillation. n (%)	21 (16)	27 (22)	4 (20)	8 (25)	60 (20)	0.584
NYHA-class ≥ III. % (n)	101 (78)	103 (83)	14 (74)	17 (53)	235 (77)	0.005
History of stroke. n (%)	18 (14)	12 (10)	4 (20)	3 (9)	36 (12)	0.613
History of CABG. n (%)	15 (12)	19 (15)	5 (25)	10 (31)	49 (16)	0.033
History of PCI. n (%)	49 (38)	53 (43)	6 (30)	10 (31)	118 (39)	0.513
History of SAVR. n (%)	4 (3)	3 (2)	0 (0)	2 (6)	9 (3)	0.581
Digoxin use. n (%)	4 (3)	5 (4)	2 (13)	0 (0)	11 (4)	0.187
Amiodarone use. n (%)	18 (14)	16 (13)	2 (13)	2 (7)	38 (13)	0.792
Access. n (%)						
Transfemoral	119 (91)	98 (79)	20 (100)	25 (78)	262 (86)	0.005
Transsubclavian	10 (8)	14 (11)	0 (0)	1 (3)	25 (8)	
Transapical	1 (1)	12 (10)	0 (0)	6 (19)	19 (6)	

Table 1. Patient characteristics. Categorical variables are displayed as counts (percentages) and differences were tested using a chi-square test for trend. Continuous variables are displayed as mean ± SD or median [IQR] and were tested with a student T-test or Mann Whitney-U test. depending on distribution. Abbreviations: CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; ES-3 = Edwards Sapien 3; ES-XT = Edwards Sapien XT; IQR = interquartile range; NYHA = New York HeartAssociation; PCI = percutaneous coronary intervention; PVD = Peripheral vascular disease; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgeons; SD = standard deviation.

variables are expressed as percentages plus absolute numbers and were tested with the chi-square test for trend. Logistic regression was performed to identify predictors for the primary outcome (i.e. PPM). THVs were included in the univariate analysis plus potential confounders in regard to the primary outcome. The number of variables in the univariate model was limited by the established rule of thumb of 10 events per variable (19). All selected variables were evaluated using univariate logistic regression for inclusion in the multivariate model, considering a P value of <0.20 as an entry criterion. These variables remained in the multivariate model, regardless of P value after adjustment. We controlled for the interaction between valve type and alternative access, because alternative access was seldom used with CoreValve and Lotus. All statistical analyses were performed with SPSS software (version 21.0.01; IBM Corp, Armonk, NY). A 2-sided value of P<0.05 was considered statistically significant.

RESULTS

A total of 2845 consecutive patients underwent TAVR at 4 European centers. For the purpose of this study, 306 (11%) patients with pre-existent RBBB (without a PPM in situ) were extracted and further analyzed (Figure 1). Patient characteristics are listed in Table 1. Mean age was 83 ± 7 years, the majority was male (194; 63%), and the median predicted risk of mortality (Society of Thoracic Surgeons (STS) score) was 6.3% (IQR 4.1–10.2). The CoreValve and Sapien-XT were used in the majority of patients (42% and 41%, respectively). An alternative access was used in ≈20% with the balloon expandable ES-XT and ES-3 and 9% with CoreValve and not with Lotus. Antiarrhythmic agents were commonly used; 13% of patients used amiodarone and 4% digoxin.

	CoreValve (N=130)	ES-XT (N=124)	Lotus (N=20)	ES-3 (N=32)	Overall (N=306)	P-value
New AV3B <24h. n (%)	48 (39)	30 (27)	13 (68)	10 (39)	101 (36)	0.004
Alternating BBB <24h*. n (%)	10 (8)	7 (6)	3 (17)	3 (12)	23 (8)	0.457
New PPM. n (%)	60 (46)	40 (32)	15 (75)	11 (34)	126 (41)	0.001
Days to PPM. median [IQR]	2 [1-5]	3 [1-5]	1 [1-2]	2 [1-5]	2 [1-5]	0.546
Indication for PPM. n (%)†						
AV3B	59 (98)	39 (97)	14 (93)	11 (100)	123 (98)	0.489
AV2B	1 (2)	0 (0)	1 (7)	0 (0)	2 (2)	
Sick sinus syndrome	0 (0)	1 (3)	0 (0)	0 (0)	1 (1)	
Ventricular paced rhythm at 30 days‡. n (%)	38 (81)	24 (92)	9 (69)	8 (73)	79 (81)	0.275
Ventricular paced rhythm at 1 year‡. n (%)	21 (91)	15 (94)	2 (67)	3 (75)	41 (89)	0.415

Table 2. Permanent pacemaker implantations and conduction related outcomes. Categorical variables are displayed as counts (percentages) and differences were tested using a chi-square test for trend. Continuous variables are displayed as median [IQR] and were tested with a Mann Whitney-U test. * Alternating bundle branch block was considered as a new left bundle branch block in this patient population with pre-existent RBBB. † Percentage indicate the proportion of patients who received a permanent pacemaker ‡ Follow-up ECGs were missing in 29 patients (23%) at 30 days and in 80 patients (64%) at 1 year. Abbreviations: AV2B = second degree atrioventricular block; AV3B = third degree atrioventricular block; BBB = bundle branch block; ES-XT = Edwards Sapien XT; ES-3 = Edwards Sapien3; IQR = interquartile range; PPM = permanent pacemaker.

Clinical Outcomes

All-cause mortality—within 48 hours following the procedure—was 3% (n=10). Thirty-day mortality rate was 7% (n=20) and 30-day stroke rate was 2% (n=5). One-year mortality rate was 18% (n=44).

PPM Implantation

Conduction changes are summarized in Table 2. The primary outcome—PPM implantation within 30 days—occurred in 41% of patients. The univariate analysis is summarized in Supplemental Table 1. The following variables were included in the multivariate analysis: valve type; alternative access; body mass index (BMI); sex; and an interaction term for valve type x alternative access (because alternative access was not applied with Lotus). Results from the multivariate analysis are displayed in Figure 2. By multivariate analysis, PPM was more common with Lotus than with the other THVs. Lotus was associated with a significantly higher PPM rate than all other individual transcatheter heart valves (Lotus versus CoreValve: odds ratio (OR), 3.69 (95% CI 1.13–12.04); P=0.030; Lotus versus ES-XT: OR 6.79 (95% CI 2.05–22.52); P=0.002; Lotus versus ES-3: OR 5.24 (95% CI 1.30–21.25); P=0.020). On the contrary, PPM rate was lower with the ES-XT valve versus CoreValve and Lotus (ES-XT vs CoreValve: OR 0.54 (95% CI 0.31–0.95); P=0.033; ES-XT vs Lotus: OR 0.15 (95% CI 0.04–0.49); P=0.002). PPM rate between the balloon expandable valves did not differ (ES-XT vs ES-3: OR 0.91 (95% C 0.40–2.07); P=0.820). Another independent predictor for PPM in the multivariable model was a higher BMI before TAVR (multivariate OR 1.08 per 1 kg/m2 increment (95% CI 1.02–1.14); P=0.013). Alternative access was associated with a lower rate of PPM in the univariate model (OR 0.32 (95% CI 0.15–0.69); P=0.004), but not in the multivariate model (OR 0.26 (95% CI 0.05–1.27); P=0.095). There was an important interaction between alternative access and valve type, attributed to the fact that Lotus was not performed with alternative access. The association between

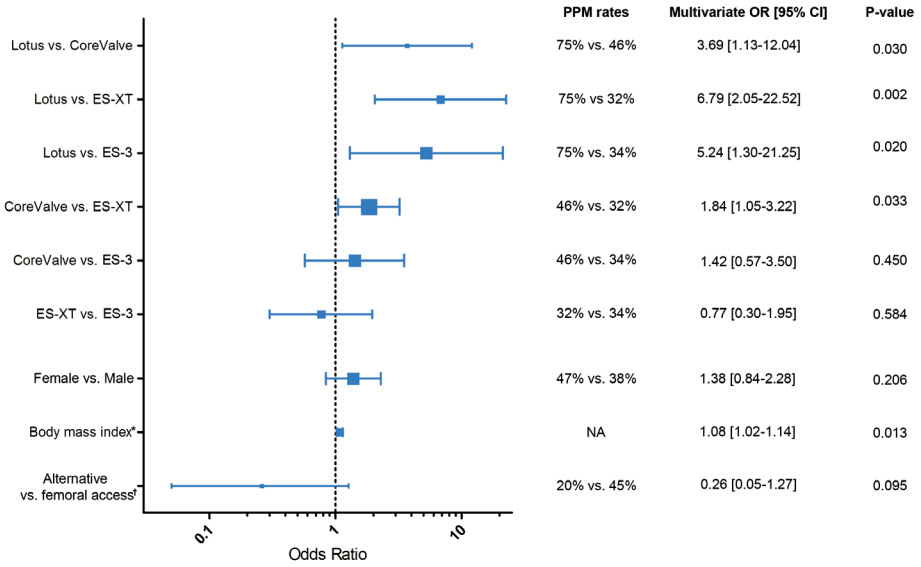

Figure 2. Forest plot displaying odds ratios (OR) for permanent pacemaker implantation after multivariate analysis. The following variables were included in the multivariate model: valve type, sex, body mass index (BMI), alternative access, and an interaction term valve type x alternative access. *Odds ratio per 1 kg/m² increment of BMI. †An interaction term for the interaction between alternative access and valve type was included in the model to adjust for the fact that alternative access was not applied with Lotus. Abbreviations: ES-3 = Edwards Sapien 3; ES-XT = Edwards Sapien XT; NA = not applicable; PPM = permanent pacemaker.

alternative access and PPM was nonsignificant with any of the valve types (CoreValve: OR 0.234 (95% CI 0.048–1.128); P=0.070; with ES-XT: OR 0.565 (95% CI 0.207–1.539); P=0.264; with ES-3: OR 0.250 (95% CI 0.0262–2.403); P=0.230).

New-Onset Conduction Disturbances

Alternating bundle branch block within 24 hours was documented in 23 patients (8%). New-onset AV3B within 24 hours was documented in 101 patients (36%). Univariate and multivariate analysis addressing new AV3B are summarized in Supplemental Table 2. New AV3B was more common with Lotus than with other individual THVs by multivariate analysis (Lotus vs ES-XT: OR 6.01 (95% CI 1.93–18.67); P=0.002; Lotus vs ES-3: OR 3.88 (95% CI 1.02–14.82); P=0.047; Lotus vs CoreValve: OR 3.80 (95% CI 1.25–11.52); P=0.018). New AV3B was less common with the ES-XT valve than with Lotus (OR 0.17 (95% CI 0.05–0.52); P=0.002). New AV3B rate between the balloon expandable valves was similar (ES-XT vs ES-3: univariate OR 0.59 (95% CI 0.24–1.43); P=0.240). Of all patients with new AV3B within 24 hours of the TAVR procedure, 91% received a PPM. One in 4 of these permanent pacemakers were implanted more than 4 days after the TAVR procedure. The documented indication for PPM implantation was almost exclusively AV3B (98%). Follow-up electrocardiograms at 30 days and 1 year confirmed ventricular pacing in 81% and 89%, respectively.

DISCUSSION

The present study showed that tailored valve choice may reduce rates of PPM implantations in patients with pre-existent RBBB. Overall PPM rate post-TAVR in patients with RBBB was 41% and was highest with Lotus (75%). More than 80% of patients with a PPM remained pacemaker dependent at 30-day and 1-year follow-up.

Prevalence of RBBB in the general population ranges from 0.5% to 1.5%, has a male predominance, and increases with age to 2.2% in patients above 55 years old (20,21). Prevalence of pre-existent RBBB is 4% in patients undergoing surgical aortic valve replacement (SAVR) with a mean age of 69 years (22), and is 10% in patients undergoing TAVR with a mean age of 81 (7). RBBB is a dominant predictor for PPM after both TAVR and SAVR (7,9,11,23,24). Not unexpectedly, patients with pre-existent RBBB are more vulnerable for high-grade AV block given that the conduction system is already impaired. With TAVR, the radial force of a stented frame may impose pressure on the conduction system embedded in the interventricular septum within a couple of millimeters from the aortic annulus and may further compromise the left bundle branch (14). Before patients with RBBB evolve toward total AV block, an alternating bundle branch can sometimes be recognized, as illustrated in Figure 3. In our population, an alternating bundle branch block within 24 hours post-TAVR could be detected in 8% of patients.

According to a recent meta-analysis, TAVR with the selfexpanding CoreValve is associated with a higher PPM rate compared with the balloon expandable ES-XT (7). PPM rate with newer-generation THVs varies and definitely remains a clinical issue, in particular with the mechanically expanded Lotus. Also, the latest balloon expandable ES-3 THV has a higher reported PPM rate compared with its predecessor, ES-XT (25).

Prevalence of RBBB in this study was similar to what has been reported in the literature. Our findings demonstrate a higher incidence of PPM in patients with pre-existent RBBB compared to what generally is reported in a random TAVR population. In patients with pre-existent RBBB treated with CoreValve in this study, almost half required a PPM as compared to 20% in the randomized US CoreValve High Risk Study and 28% in the meta-analysis by Siontis et al (7,26). PPM rate in patients with ES-XT was 31% and is significantly higher than the 6% in the meta-analysis and 9% in the randomized PARTNER 2 (Placement of Aortic Transcatheter Valves 2) trial (3). In our study, also with newer generation THVs in patients with pre-existent RBBB, the PPM rate was consistently higher than what is reported in high-risk TAVR patients: ES-3 34% versus 10% (27) and Lotus 75% versus 27% (9), respectively.

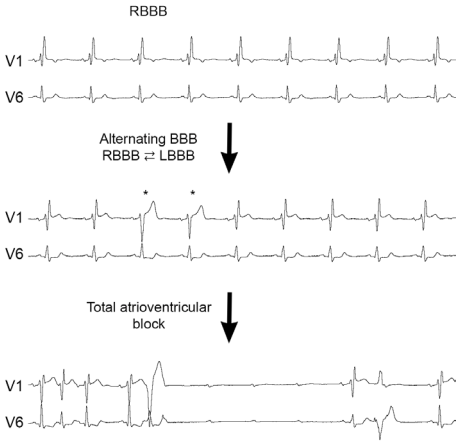

Figure 3. Two-lead electrocardiogram derived from continuous rhythm monitoring within 24 hours after transcatheter aortic valve replacement, illustrating the typical cascade from RBBB to a total atrioventricular block. *Intermittent sinus beats with LBBB. Abbreviations: BBB = bundle branch block; LBBB = left bundle branch block; RBBB = right bundle branch block.

Multivariate analysis confirmed a higher incidence of PPM with Lotus than with other THV designs. Conversely, ES-XT was associated with the lowest PPM risk. Interestingly, a higher BMI before TAVR also predicted PPM implantation, although the effect was modest. Previous studies reported the impact of BMI on outcomes post-TAVR, but did not show an enhanced rate of PPM implantations (4,28). The exact pathophysiology is unclear. However, BMI may pose particular hurdles from a procedure execution perspective and maybe result in less accurate (and maybe deeper) valve implants. Alternative access (i.e. transsubclavian or transapical access) was associated with a lower PPM rate in the univariate model. However, this effect was absent in the multivariate model, suggesting the effect of the balloon expandable valves that were used in the majority (75%) of alternative access procedures.

The high rate of PPM with Lotus could hypothetically be caused by (1) a higher radial force of the stented frame compared to other THVs, which potentially forces the native annulus in a circular shape, and (2) the Lotus frame remains in contact with the wall of the left ventricular outflow tract throughout the process of foreshortening and locking, which could be more harmful to the conduction system. Depth of transcatheter valve implantation is an established predictor for CoreValve, ES-XT, and ES-3 (29-31), in particular with an implantation depth of more than 6 mm below the native aortic valve. Methodology to determine depth of implantation is not standardized and was not collected in this study. However, depth of implantation could affect the need for PPM with any THV and warrants further detailed analysis.

Previous reports suggested the transient nature of TAVR induced conduction disorders given that up to half of patients with new pacemakers post-TAVR were no longer pacemaker dependent at follow-up (13,32,33). In contrast, our study demonstrates a paced rhythm in 89% of patients at 1 year in patients who received a PPM, underscoring a less-resilient conduction system in these patients. Similarly, patients with pre-existent RBBB who developed AV3B within 24 hours after the procedure received a PPM in 91% of the cases, with 1 in 4 receiving the pacemaker more than 4 days post-TAVR, underscoring the

persistence of this conduction disorder. In aggregate, conduction recovery post-TAVR in patients with pre-existent RBBB is unlikely, and therefore the decision to proceed with PPM implantation could be made early after TAVR to minimize hospital stay.

In our study—involving patients with pre-existent RBBB and a relatively high rate of PPM implantations—the mortality rate (7% at 30 days and 18% at 1 year) is on par with recently published trials and registry data (26,31,34-38). Conflicting data link new conduction disorders in general and PPM implantation in particular to impaired TAVR-related outcome, including less improvement in LV function or quality of life, more rehospitalizations, and increased 1-year mortality (13,39-41). Hypothetically, PPM implantation in patients with RBBB levels out mortality attributed to the high incidence of - potentially lethal - total heart blocks.

Limitations

This multicenter study has an observational design and may suffer from inherent bias in terms of THV selection and confounders. Depth of implantation—which is known to be associated with PPM—was not collected in this study. Indeed, given that balloon expandable devices have less TAVR-related conduction disorders, operators may already favor this THV for patients with pre-existent RBBB and avoid mechanically expanded valves on the other hand. Nonetheless, only THVs with at least 10 patients in the database were eligible for further analysis, and the number of events was sufficient to allow for adequate multivariate analysis to adjust for confounders. We acknowledge that the Lotus valve is relatively under-represented in the present study, and therefore avoidance of this valve cannot be strongly recommended. However, we believe that there is a clear signal that this valve is associated with the highest PPM rate. The decision to implant a PPM was at the treating physician's discretion, but was most often for high-degree AV block and thus conforms to current international guidelines (17).

CONCLUSION

Postprocedural PPM rate in this cohort of patients with pre-existent RBBB was consistently higher than described in the literature for all THVs. PPM rate was highest with Lotus and lowest with the balloon expandable ES-XT and ES-3. Pacemaker dependency remained high at both 30-day and 1-year follow-up.

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SUPPLEMENTAL MATERIAL

	Univariate OR [95% CI]	P-Value
Type of THV		
Lotus vs. CoreValve	3.50 [1.20-10.20]	0.022
Lotus vs. ES-XT	6.30 [2.14-18.55]	0.001
Lotus vs. ES-3	5.73 [1.65-19.94]	0.006
CoreValve vs. ES-XT	1.80 [1.08-3.00]	0.024
CoreValve vs. ES-3	1.64 [0.73-3.67]	0.232
ES-XT vs. ES-3	0.91 [0.40-2.07]	0.820
Patient characteristics		
Alternative access	0.32 [0.15-0.69]	0.004
Baseline atrial fibrillation	0.79 [0.44-1.42]	0.429
Body mass index*	1.08 [1.02-1.14]	0.006
Female gender	1.49 [0.93-2.39]	0.098
Medication Amiodarone	0.87 [0.43-1.75]	0.690
Medication Digitalis	0.86 [0.25-3.00]	0.813
NYHA - class ≥ III	0.92 [0.54-1.58]	0.765
Prior SAVR	0.40 [0.08-1.95]	0.256

Supplemental Table 1. Predictors for permanent pacemaker by univariate logistic regression. Variables in italic were included in the multivariate analysis. *Odds ratio per 1 kg/m2 increment of body mass index. Abbreviations: CI = confidence interval; ES-3 = Edwards sapien valve 3; ES-XT = Edwards Sapien XT; NYHA = New York Heart Association; SAVR = surgical aortic valve replacement; THV = transcatheter heart valve.

	Univariate OR [95% CI]	P-Value	Multivariate OR [95% CI]	P-Value
Type of THV				
Lotus vs. CoreValve	3.43 [1.22-9.63]	0.019	3.80 [1.25-11.52]	0.018
Lotus vs. ES-XT	5.92 [2.06-16-99]	0.001	6.01 [1.93-18.67]	0.002
Lotus vs. ES-3	3.47 [0.99-12.09]	0.051	3.88 [1.02-14.82]	0.047
CoreValve vs. ES-XT	1.73 [0.99-3.00]	0.053	1.58 [0.88-2.85]	0.128
CoreValve vs. ES-3	1.01 [0.42-2.41]	0.981		
ES-XT vs. ES-3	0.59 [0.24-1.43]	0.240	0.17 [0.05-0.52]	0.002
Patient characteristics				
Alternative access	0.51 [0.21-1.23]	0.133	0.48 [0.13-1.81]	0.281
Baseline atrial fibrillation	1.00 [0.53-1.86]	0.987		
Body mass index	1.04 [0.99 -1.10]	0.126	1.04 [0.98-1.10]	0.218
Female gender	1.39 [0.84-2.29]	0.200	1.30 [0.77-2.20]	0.326
Prior surgical aortic valve replacement	0.89 [0.22-3.63]	0.868		

Supplemental Table 2. Predictors for new total atrioventricular block <24h. Results from uni- and multivariate logistic regression for new onset third degree atrioventricular block within 24 hours. Variables in italic were included in multivariate regression. Abbreviations: CI = confidence interval; ES-XT = Edwards Sapien XT; ES-3 = Edwards Sapien 3; OR = Odds Ratio; THV= transcatheter heart valve.

CHAPTER IV

Conduction dynamics after transcatheter aortic valve implantation and implications for permanent pacemaker implantation and early discharge: the CONDUCT-study

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ABSTRACT

Aims

To correlate dynamics in electrical conduction after transcatheter aortic valve implantation (TAVI) with need for permanent pacemaker implantation (PPM) and assess implications for early discharge.

Methods

Daily ECG's after TAVI were analyzed for rhythm and conduction times and were correlated with PPM.

Results

TAVI was performed in 291 consecutive patients with three contemporary transcatheter heart valve designs: Medtronic CoreValve (n=111), Edwards Sapien XT (n=29) and Sapien 3 (n=72), and Boston Lotus (n=79). We considered two cohorts: A. Patients with normal baseline conduction; and B. patients with pre-existent conduction disturbances. Based on QRS dynamics, three patterns were discerned: stable normal QRS duration, transient QRS prolongation and persistent QRS prolongation. In cohort B QRS dynamics did not correlate with PPM. In contrast, in cohort A QRS dynamics and PPM appeared highly correlated. Neither patients with stable normal QRS duration (0/47), nor patients with transient QRS prolongation required PPM (0/26). All PPMs occurred in patients with persistent QRS prolongation until discharge (27/85). Persistent QRS prolongation was typically seen with Lotus and CoreValve, whereas stable normal QRS duration was typically seen with Sapien XT and Sapien 3.

Conclusion

Three distinct patterns of QRS dynamics can be discerned after TAVI and their predictive probabilities for PPM strongly relate to the baseline conduction status. Patients with normal conduction at baseline and stable QRS duration after TAVI are potentially eligible for early discharge.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has evolved into an attractive, minimally invasive alternative to surgical aortic valve replacement for patients with severe aortic stenosis and intermediate or greater surgical risk (1-3). Not only the procedure itself, but also hospital stay has shortened to extremes of same day discharge in some instances (4). Electrical conduction disturbances and need for permanent pacemaker implantation (PPM) are frequent after TAVI (5), and imposes an important obstacle for early discharge after TAVI.

Conduction disturbances are more common with self-expanding and mechanically expanded transcatheter heart valves (THVs) compared to balloon-expandable valves (6, 7). Apart from THV design, several baseline predictors for post-procedural conduction disturbances have been identified (e.g. pre-existing conduction disturbances, excessive device oversizing relative to the annular root dimensions, and depth of implantation) (6, 8).

Newly acquired conduction disturbances do not always persist since half of patients who received a PPM are no longer pacemaker-dependent at long-term follow up (8, 9). Therefore the decision for either safe early discharge or monitoring by telemetry and potential PPM implantation poses a current challenge.

Electrical conduction after TAVI may be dynamic and device dependent. Proper understanding of these dynamics is clinically relevant and may help guide patient management and facilitate early discharge. The ECG immediately after TAVI already provides information to determine whether patients might be eligible for early discharge (10). The purpose of the present study was to assess conduction times (i.e. QRS-duration) during the entire admission after TAVI, in order to identify dynamic patterns and to correlate with need for permanent pacemaker dependency.

METHODS

All consecutive patients who underwent transarterial (transfemoral or transsubclavian) TAVI between January 2012 and December 2015 in our center were entered in a prospective database. This study complied with the Declaration of Helsinki. All patients provided written informed consent for the procedure and data analysis for research purposes per Institutional Review Board approval. This study was not subject to the Dutch Medical Research Involving Human Subjects Act, which was confirmed by the local medical ethics committee of the Erasmus MC Rotterdam.

An overview of inclusion is illustrated in Figure 1. Patients who died within 72 hours after the procedure were excluded from the analysis. Three THV-designs were used: Corevalve (n=111) (Medtronic, Minneapolis, Minnesota),

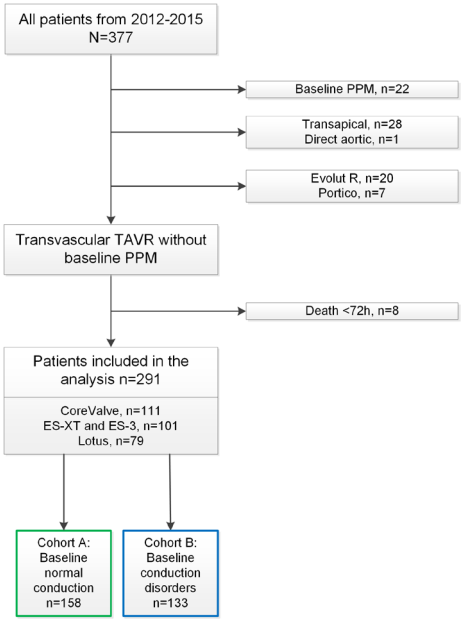

Figure 1. Flowchart of study inclusion. Abbreviations: ES-XT = Edwards Sapien XT; ES-3 = Edwards Sapien 3; PPM = permanent pacemaker implantation.

Sapien XT (n=29) and Sapien 3 (n=72) (Edwards Lifesciences, Irvine, California), Lotus (n=79) (Boston Scientific Corporation, Marlborough, Massachusetts).

For the purpose of this study, we considered two cohorts: cohort A consisted of patients with untainted conduction, whereas cohort B consisted of patients with pre-existent conduction disturbances (i.e. 1st or degree AV-block, hemiblock or bundle branch block).

Twelve-lead ECGs were collected prior to TAVI and daily afterwards up to discharge to a maximum of 14 days and at one-month follow-up at the outpatient clinic visit. ECGs were interpreted by dedicated clinical researchers (LVG, HK and YA). If necessary, an experienced cardiologist (NVM) was consulted for consensus. The ECGs were analyzed for rhythm, conduction times, and the presence of AV block or bundle branch block. Conduction times were derived from digitalized ECGs with a chart speed of 25mm/s. Computer-calculated conduction times were used, since they show less variability compared to manual caliper methods (11). Only ECGs without pacemaker intrusion were included in our analysis. In presence of multiple ECGs on the same day, the ECG with the longest calculated QRS-duration was selected.

QRS-prolongation of 20 ms was considered a significant change. Three conduction patterns were discerned: (1) Stable: QRS-duration after TAVI did not prolong by > 20 ms; (2) Transient: QRS duration after TAVI prolonged by > 20 ms but at the discharge ECG the QRS duration narrowed again within 20 ms; (3) Persistent: QRS duration after TAVI prolonged by > 20 ms and the QRS duration at discharge persisted at least 20 ms beyond baseline.

The primary outcomes of this study were 1. New onset high degree AVB and 2. need for PPM. The decision for PPM was per treating physician's discretion, although agreed by an electrophysiologist and in general in compliance with contemporary ESC Guidelines on PPM (12). Patients who receive a permanent pacemaker in our institution systematically visit the pacemaker technician at 10 days and 6 months after implantation at the outpatient clinic. At 10 days the anterograde and retrograde properties of the atrioventricular conduction are assessed with pacing maneuvers, after which the pacemaker settings are adapted in order to prioritize the native conduction system. A PPM interrogation at 6 months assesses pacing percentage. For the purpose of this study, patients with less than 20% ventricular pacing over 6 months of follow-up – which is suggestive for independency of ventricular pacing (13) - were then re-adjudicated by an electrophysiology expert (DT) for pacemaker dependence. Depending on whether there was normal intrinsic atrioventricular conduction pacing was labeled as 'dependent' or 'independent'.

Continuous variables were presented as mean (±SD) or median (interquartile range). The distribution of continuous variables was assessed for normality with histograms and the Shapiro-Wilk test. Comparisons between the ECG conduction patterns for repeatedly measured continuous variables were done using a repeated measures analysis of variance (ANOVA) with post-hoc Tukey adjustment. The assumption of homogeneity of variances was tested with the Levene's test. Categorical variables were expressed as absolute counts plus percentages and were compared by use of the Pearson's square test and Z-test for proportions.

All statistical analyses were performed with SPSS version 21.0.1 (IBM Corp, Armonk, NY). A two-sided value of $P<0.05$ was considered statistically significant.

RESULTS

A total of 291 consecutive patients underwent transfemoral (94%) or transsubclavian (6%) TAVI with CoreValve (38%%), Sapien XT or Sapien 3 (35%), or Lotus (27%). Mean age was 79 ± 8 years, 46% were female. Balloon predilatation was performed in 51% of patients. Half of the patients (54%) did not have pre-existent conduction disturbances (cohort A) whereas the other half (46%) did (cohort B). Baseline characteristics between cohort A and B were well balanced (Table 1). AV1B was the most common conduction disturbance (21%), followed by left anterior fascicular block (16%), left bundle branch block (12%) and right bundle branch block (11%).

		Cohort A (N=158)	Cohort B (N=133)	Overall (N=291)	P-value
Age in years		78 ± 8	80 ± 7	79 ± 8	0.116
Male gender		77 (49%)	79 (59%)	156 (54%)	0.069
Body mass index in kg/m2		27 ± 5	27 ± 5	27 ± 5	0.860
Body surface area in m2		1.86 ± 0.20	1.86 ± 0.20	1.86 ± 0.20	0.966
Creatinin level in µmol/L		99 [74-128]	94 [77-117]	96 [77-122]	0.463
Renal dialysis		7 (5%)	4 (4%)	11 (4%)	0.759
DM		50 (32%)	48 (36%)	98 (34%)	0.424
Hypertension		134 (85%)	104 (78%)	238 (82%)	0.145
Log EuroSCORE in %		11 [7-18]	12 [9-19]	12 [8-19]	0.102
NYHA-class	I	4 (3%)	3 (2%)	7 (3%)	
	II	36 (24%)	28 (23%)	64 (23%)	0.987
	III	95 (63%)	80 (65%)	175 (64%)	
	IV	16 (11%)	12 (10%)	28 (10%)	
Atrial fibrillation		48 (30%)	32 (24%)	80 (28%)	0.229
Conduction disturbance*	None	158 (100%)	0 (0%)	158 (54%)	
	AV1B	0 (0%)	61 (46%)	61 (21%)	
	LBBB	0 (0%)	35 (27%)	35 (12%)	NA
	RBBB	0 (0%)	33 (25%)	33 (11%)	
	LAFB	0 (0%)	47 (35%)	47 (16%)	
	LPFB	0 (0%)	6 (5%)	6 (2%)	
Access	Transfemoral	152 (96%)	122 (92%)	274 (94%)	0.105
	Transsubclavian	6 (4%)	11 (8%)	17 (6%)	
Predilatation		79 (50%)	70 (53%)	149 (51%)	0.651
THV	CoreValve	58 (37%)	53 (40%)	111 (38%)	0.813
	ES-XT or ES-3	55 (35%)	46 (35%)	101 (35%)	
	Lotus	45 (49%)	34 (26%)	79 (27%)	

Table 1. Baseline characteristics. Categorical variables are displayed as counts (percentages. Continuous variables are displayed as mean ± SD or median [interquartile range]. * Patients without conduction disturbances at baseline represent Cohort A and patients with conduction disturbances represent Cohort B. Abbreviations: CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; MI = myocardial infarction; PCI = percutaneous coronary intervention; THV = transcatheter heart valve.

Conduction related outcomes are displayed in Table 2. Intraprocedural LBBB and high degree AVB were common (67% and 33%, respectively). Delayed high degree AVB (i.e. high degree AVB that first presented after the patients had left the catheterization laboratory) occurred in 8% of patients. At 30-days, overall 23% required PPM; 17% in cohort A compared to 29% in cohort B (p=0.013). Indication for PPM was almost exclusively a high degree AVB (94%). None of the patients had a documented high degree AVB after discharge nor did any of them need a PPM during 1-year follow-up. In the majority, the percentage of pacing that was provided was either less than 10% or more than 90% of the time (Table 2, Supplemental Figure 1). Pacemaker interrogations at 6 months follow-up were completed in 74% of patients (17 patients were lost to follow-up). The interrogation revealed <20% paced rhythm (i.e. pacemaker independent) in 39% of patients. The amount of ventricular pacing did not differ between cohort A and B (p=0.459).

		Cohort A (N=158)	Cohort B (N=133)	Overall (N=291)	P-value
Number of days to discharge		8 [6-11]	8 [6-12]	8 [6-11]	0.905
Thirty day mortality		8/157 (5%)	6/133 (5%)	14/290 (5%)	0.817
One year mortality		23/151 (15%)	19/121 (16%)	42/272 (15%)	0.915
Intraprocedural new LBBB		105/133 (74%)	48/84 (57%)*	153/217 (67%)	0.007
Intraprocedural new AV3B		35/133 (25%)	47/133 (43%)	82/291 (33%)	0.002
PPM at 30 days†	All THVs	27/158 (17%)	39/133 (29%)	66/291 (23%)	0.013
	CoreValve	15/58 (26%)	16/53 (30%)	31/111 (28%)	0.621
	ES-XT or ES-3	5/55 (9%)	11/46 (24%)	16/101 (16%)	0.042
	Lotus	7/45 (16%)	12/34 (35%)	19/79 (24%)	0.042
Indication for PPM‡	High degree AVB	26/27 (96%)	36/39 (92%)	62/66 (94%)	
	Sick sinus syndrome	1/27 (4%)	2/39 (5%)	3/66 (5%)	0.094
	Trifascicular block	0/27 (0%)	1/39 (3%)	1/66 (2%)	
Number of days to PPM		6 [1-8]	4 [1-8]	5 [1-8]	0.377
Percentage pacing at 6 months interrogation§	0%	2/22 (9%)	4/27 (15%)	6/49 (12%)	
	1-20%	7/22 (32%)	6/27 (22%)	13/49 (27%)	0.459
	21-99%	6/22 (27%)	12/27 (44%)	18/49 (37%)	
	100%	7/22 (32%)	5/27 (19%)	12/49 (25%)	

Table 2. Conduction related and clinical outcomes. Categorical variables are displayed as counts (n/N) (percentages. Continuous variables are displayed as median [interquartile range]. * patients with LBBB at baseline are herein excluded.† N is total number of patients treated with that particular valve. ‡ N is total number of patients with a PPM. §Pacemaker interrogations were performed in 49 of 66 patients (17 patients were lost to follow-up).

In cohort A, conduction patterns correlated with PPM, regardless of THV type (Figure 2). In cohort B, high degree AVB and PPM appeared unrelated to QRS patterns (Figure 3).

Changes in QRS duration for the three discerned patterns in cohort A are displayed in Supplemental Table 4 and Figure 2. In patients with a stable QRS duration, the mean QRS duration at baseline was 95 ± 11 ms. In patients with transient QRS prolongation, mean QRS duration at baseline was 100 ± 9 ms and prolonged up to 144 ± 15 ms, after which it narrowed to 103 ± 10 ms at discharge. On aggregate, mean QRS duration at follow-up was 102 ± 11 ms. In patients with persistent QRS prolongation, the mean QRS duration at baseline was 97 ± 11 ms and prolonged up to 157 ± 15 ms and it remained broad (152 ± 17) until discharge. At follow-up, the QRS-duration was still broad (137 ± 23 ms). It took 1 day to reach the maximum QRS duration in the majority of patients (61%) irrespective of THV design or the transient or

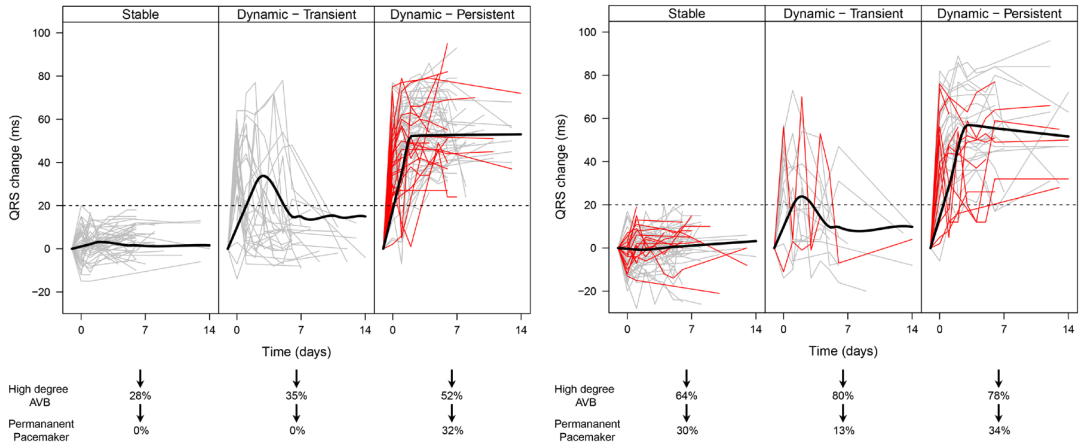

Figure 2 and Figure 3 . Dynamics of QRS-duration in cohort A (left) (i.e. patients with normal conduction atbaseline) and cohort B (right)(i.e. patients with conduction disturbances at baseline), with associated high degree AVB and PPM rates. QRS-interval times are plotted as a difference from baseline up to 14 days after TAVI (depending on date of discharge). The grey lines represent individual patients who did not require PPM, red lines represent patients who required PPM, and the bold black line is a smoothed line that connects mean QRS durations to reflect the general trend of the groups. Abbreviations: AVB = atrioventricular block; ms = milliseconds.

persistent nature (Transient: 0.5 (IQR 0-4) day; Persistent: 1 (IQR 0-3) day). The transient pattern became apparent at 1 day post TAVI (IQR 1-4), and the QRS interval normalized up to day 6.

Implantation of a Lotus valve was typically followed by persistent QRS prolongation (69%), in contrast to stable normal QRS duration (7%) or transient QRS prolongation (24%). Conversely, half of the patients treated with the Sapien XT and Sapien 3 had a stable normal QRS duration (51%) compared to transient QRS prolongation (13%) and persistent QRS prolongation (36%). With CoreValve, persistent QRS prolongation was most common (57%) in contrast to stable normal QRS duration (28%) or transient QRS prolongation (16%).

In cohort A, patients with a stable normal QRS duration and patients with transient QRS prolongation never required a PPM, although high degree AVB appeared and resolved in 28% and 35%, respectively. In patients with a persistent QRS prolongation high degree AVB appeared in 52% (44/84) and 32% (27/84) required a PPM. At the 6-month pacemaker interrogation 41% was independent of their pacemaker.

QRS-patterns determined at daily intervals and subsequent conduction related events are listed in Supplemental Figure 2. Patients with a stable normal QRS pattern 1 day post TAVI have a low likelihood for high degree AVB or PPM with pacemaker dependency. Conversely, patients with a transient/persistent QRS prolongation may develop high degree AVB or pacemaker dependency up to day 6.

Mortality at 30-days and 1-year were 5% and 15% respectively, and were similar between cohort A and B. Supplemental Table 2 shows an overview of death causes during 1 year follow-up. Notably, one-year mortality in patients from cohort A with stable conduction occurred in 7 patients in total, and none were related to late conduction disorders. These deaths were caused by cerebral stroke, hepatic failure, hospital-acquired pneumonia, sepsis, terminal heart failure, rectum carcinoma and in one patient the cause was unknown.

DISCUSSION

The present study demonstrates that QRS dynamics following TAVI may have clinical implications. The main findings can be highlighted as follows: 1) Three distinct patterns of QRS dynamics can be identified after TAVI: stable normal QRS-duration, transient QRS-prolongation and persistent QRS-prolongation. 2) Patients with newly acquired QRS prolongation after TAVI require longer telemetric monitoring than those with stable normal QRS duration and if persistent they have a high need for PPM. 3) In patients with pre-existing conduction disturbances before TAVI, high degree AVB and PPM occur irrespective of QRS dynamics. 4) QRS prolongation typically peaks within 1 day after TAVI. 5) Balloon expandable TAVI is associated with more stable QRS duration. 6) Up to 40% of patients are no longer pacemaker dependent during follow up.

The vicinity of the atrioventricular His bundle to the aortic valve contributes to the risk for conduction disturbances and PPM after aortic valve replacement in general and TAVI in particular (5, 14). Past research has mainly focused on baseline predictors of conduction disturbances (6, 8), enabling to identify those patients who are at high risk for PPM. In addition, choice of THV is a main contributor, as PPM rates are consistently higher with the self-expanding CoreValve, reported to be ~30% (15, 16) compared to 10-15% with the balloon-expandable Sapien XT and Sapien 3 (15-17) and ~30% with the mechanically expanded Lotus (7).

Currently, daily practice is proceeding rapidly by discharging patients early at the expense of missing emerging conduction disorders (4). In the present study QRS-prolongation typically peaked within 1day after TAVI. Patients with normal baseline conduction and stable QRS duration or transient QRS prolongation never required PPM. When observed at daily intervals it appears that a stable QRS duration 1 day post TAVI may justify safe early discharge. The opposite is true for patients with normal baseline conduction and persistent QRS prolongation, since they are at risk for high degree AVB, which impedes early discharge. Therefore our data strongly recommends to keep these patients admitted on telemetric monitoring for a minimum of 6 days. We hypothesize that a persistent QRS-prolongation may identify more permanent and explicit damage to the atrioventricular bundles.

On the other hand, in patients with pre-existent conduction disturbances QRS prolongation can be deceiving, since patients with stable QRS duration and transient QRS prolongation also required PPM in the present study. Therefore patients with pre-existent conduction disorders have an eminent risk for PPM and thus warrant longer telemetric monitoring.

Recently, Toggweiler et al. reported that ECGs after TAVI can be helpful to identify patients who need telemetric monitoring (10). The authors concluded that patients without conduction disorders or a stable ECG for 48 hours after TAVI can be safely discharged. Our data may refine this concept by adding that patients with pre-existent conduction disturbances (i.e. prior to TAVI) may need longer clinical observation to rule out need for PPM.

In patients with normal conduction at baseline, QRS prolongation – either persistent or transient – was more frequent with CoreValve and Lotus. This is consistent with the higher reported PPM rates with these devices. It is intriguing that QRS-prolongation occurred less with balloon-expandable valves, suggesting patients treated with these devices are more suitable for early discharge (provided that other complica-

tions have been ruled out).

Whether TAVI patients remain pacemaker dependent is subject of ongoing debate. QRS prolongation after TAVI is sometimes transient as in more than one third of the patients bundle branch blocks recover (8). Pacemaker rhythm on follow-up ECGs can give a rough impression for at least partial pacemaker dependency. Data from the PARTNER-trial reported ventricular paced rhythm in 50% of patients 30-days after TAVI(8). Moreover, at 1-year follow-up more than half of the patients appear no longer pacemaker dependent (9). Outside the field of TAVI, the 'Inhibition of Unnecessary RV Pacing With AVSH in ICDs'-study (INTRINSIC RV) aimed to inhibit the rate of unnecessary right ventricular pacing with implantable cardioverter defibrillators. The authors reported that patients with less than 20% right ventricular pacing had 0% pacing when switched to VVI-mode (13). Unnecessary pacing is mostly related to premature atrial and ventricular contractions or pacemaker dysfunction (18), which implicates that 0% pacing is rare, even in patients with normal conduction. In the present study, 41% of the patients with a permanent pacemaker were paced less than 20% during 6 months follow-up. Dedicated interrogation of these pacemakers revealed that none of these patients were truly pacemaker dependent at follow up. This supports the theory that the threshold for PPM after TAVI may be (too) low. Future devices may enable continuous rhythm monitoring at home in the form of self-adhesive patches, with wireless transmission to the physician (19). This may be a cost-effective way for safe early discharge and avoiding needless PPM.

Our findings may have clinical implications. PPM in the elderly is not harmless, for early complications are common in patients above 75 years (5%) (20). Most frequent complications include lead dislodgement/loss of capture, pneumothorax and infection. Moreover, unnecessary right ventricular pacing may contribute to heart failure.

The rate of delayed high degree AVB in the present study was similar to what has been reported by Toggweiler et al. (Figure 4). In addition, newly acquired QRS prolongation that persisted for 6 days announced events that would oppose safe discharge in 12% of patients with normal QRS at baseline and underscores the importance of prolonged telemetric monitoring. Duration of telemetric monitoring and timing for safe discharge in patients with newly acquired or pre-existing conduction disorders requires further study and validation in a larger prospective cohort.

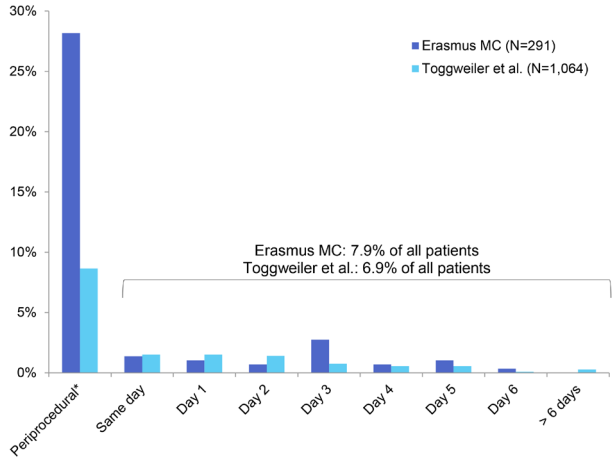

Figure 4. Overview of first presentation of high degree AVB in the present study and the study by Toggweiler et al (10). * Note that in the present study high degree AVB during the procedure was also noted, whereas the study by Toggweiler et al. only noted high degree AVB present at the moment the patient left the catheterization laboratory.

Limitations

This was a single-center observational study and may suffer from inherent bias. Pre-existent conduction disorders were not equally distributed among different THVs and combinations of various conduction

disorders were present. Our study represents a real world TAVI population and it therefore enhances generalizability. The decision to implant a PPM was at the treating physician's discretion but was almost exclusively high degree AVB and thus conform current international guidelines (12). ECG with analyzable conduction times (i.e. not intruded by a ventricular pacing) was available for 66% of total hospitalized days and was thus incomplete, yet reflects retrospective analysis of current clinical practice. Our study represents the most elaborate sample of conduction times after TAVI reported to date. The missing ECGs were equally distributed over time and among the different devices and conduction patterns, therefore we believe the described patterns are valid.

CONCLUSIONS

Three distinct patterns of QRS dynamics can be discerned after TAVI and their predictive probabilities strongly relate to the baseline conduction status. Patients with normal conduction before and after TAVI do not develop need for PPM and may be pre-eminently eligible for early discharge. Patients with pre-existing or newly acquired QRS prolongation need prolonged telemetric monitoring because need for PPM is high.

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SUPPLEMENTAL MATERIAL

	Stable (n=47)	Dynamic transient (n=26)	Dynamic persistent (n=85)	P-value
Baseline QRS duration	95 ± 11	100 ± 9	97 ± 11	0.129
Δ QRS baseline – maximum	+8 ± 6*	+48 ± 16	+57 ± 15	<0.001
Δ QRS maximum – discharge	-3 ± 6	-45 ± 17*	-6 ± 12	<0.001
Δ QRS discharge – follow-up 30 days	-5 ± 6	-1 ± 10	-15 ± 20*	<0.001
Δ QRS baseline – follow-up 30 days	0 ± 5	+3 ± 9	+39 ± 23*	<0.001
Follow-up 30 days QRS duration	98 ± 10*	102 ± 11*	137 ± 23*	<0.001

Supplemental table 1. QRS dynamics from baseline to 30 days follow-up in Cohort A. * denotes significant differences compared to both other subgroups at a p<0.05 confidence level.

	Cohort A		Cohort B	
	PPM +	PPM -	PPM +	PPM -
Mortality at 30 days	1 / 27 (4%)	7 / 130 (5%)	1 / 39 (3%)	5 / 94 (5%)
Mortality at 1 year*	1 / 26 (4%)	22 / 125 (18%)	7 / 36 (18%)	12 / 85 (13%)
Death cause	- Stroke	- Sepsis (2x)	- Sepsis	- Sepsis
		- Multi-organ failure	- Subdural hematoma	- Stroke (2x)
		- Pneumonia (2x)	- Pneumonia	- Multi-organ failure
		- Stroke (3x)	- Unknown (4x)	- Hemothorax
		- Pulmonary embolism		- Valve embolization
		- Liver cirrhosis		- Colitis
		- Heart failure		- Liver cirrhosis
		- Cancer (2x)		- Unknown (4x)
		- Myocardial infarction		
		- Unknown (8x)		

Supplemental table 2. Overview of death causes during follow-up for Cohort A and B. Incidence is shown as counts (n/N) and percentages. *19 patients were lost to follow-up. Abbreviatons: PPM = permanent pacemaker implantation.

CHAPTER V

Importance of the left ventricular outflow tract in the need for pacemaker implantation after transcatheter aortic valve replacement

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ABSTRACT

Background

The interaction of left ventricular outflow tract (LVOT) and transcatheter heart valve (THV) is complex and may be device design specific. We sought to study LVOT characteristics and its relation with permanent pacemaker implantation (PPI) after transcatheter aortic valve replacement (TAVR).

Methods

We studied 302 patients with a median age of 81 years (IQR 75–84). Computed tomography was used to assess LVOT in terms of amount of calcium, perimeter and device size relative to LVOT.

Results

We implanted a Medtronic CoreValve (MCS) in 203 patients, Edwards-Sapien XT (ESV-XT) in 38, Edwards-Sapien S3 (ESV-S3) in 26 and Lotus in 35 patients. Sixty-eight patients (22.5%) received a new PPI within 30 days after the index procedure. The incidence of PPI was 22.7% with MCS, 10.5% with ESV-XT, 26.9% with ESV-S3 and 31.4%with Lotus. By multivariate analysis RBBB at baseline (OR 2.9 (95% CI 1.2–6.9, p=0.014), second generation valves (OR 2.1 (95% CI 1.0–4.5), p=0.048), DOI (OR 1.20 per 1 mm increment, (95% CI 1.09–1.31), $p < 0.001$) and LVOT sizing (OR per 1% increment 1.03 (95% CI 1.01–1.07), p=0.022) were associated with need for PPI. Sensitivity analyses suggest that a lesser degree of LVOT oversizing triggers PPI with second generation THVs vs. first generation THVs.

Conclusions

More LVOT oversizing is associated with a higher need for permanent pacemaker implantation after TAVR, even more so with deeper THV implants and next generation devices (ESV-S3 and Lotus). Sizing algorithms should focus more on LVOT dimensions to reduce PPI.

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is increasingly adopted for treatment of symptomatic severe aortic stenosis (AS) (1-5). Compared to surgical aortic valve replacement (SAVR) TAVR is associated with a higher need for permanent pacemaker implantation (PPI) with frequencies varying from 2 to 51% (4,6,7). PPI leads to prolonged in-hospital stay, more repeat hospitalizations and less improvement in quality of life (7). The atrioventricular bundle of His is located in the left ventricular outflow tract (LVOT) close to the native aortic valve. This proximity exposes the AV conduction system to all kinds of TAVR associated trauma from wires, balloons and transcatheter heart valves (8,9). LVOT calcium content and its size relative to the implanted transcatheter heart valve (THV) combined with the degree of THV protrusion into the LVOT may affect the underlying conduction system and consequently the need for PPI. This interaction of LVOT and THV is complex and may be THV design dependent. Newer THV designs (Figure 1) were developed to facilitate the TAVR procedure in general and reduce the frequency of paravalvular aortic regurgitation, yet need for PPI may be higher (10,11). The aim of this study is therefore to determine to what extent the LVOT phenotype is associated with need for PPI and whether this correlation varies between first-generation and second/next generation valves.

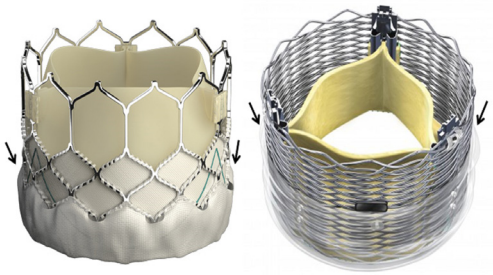

Figure 1. Next generation valves: left Edwards-SAPIEN 3 and right Boston Sadra Lotus. Both have one cuff/skirt (arrows) designed to avoid paravalvular regurgitation, increasing thewidth of the frame at the inflow level.

METHODS

Patients

This study included all patients who underwent TAVR in our center from November 2005 to January 2015 (N = 504) and had multimodality imaging planning with transthoracic echocardiography and multi-slice computed tomography (MSCT) assessment of the aortic valve and peripheral arterial tree (Figure 2). A multi-disciplinary heart team consisting of at least 1 cardio-thoracic surgeon and 1 interventional cardiologist judged all patients at high risk for mortality with SAVR. TAVR procedure was performed under general anesthesia using standard techniques as described (12). Relevant clinical and procedural data were prospectively collected and entered in a dedicated database. All patients provided written informed consent for the procedure and data analysis for research purposes per Institutional Review Board approval.

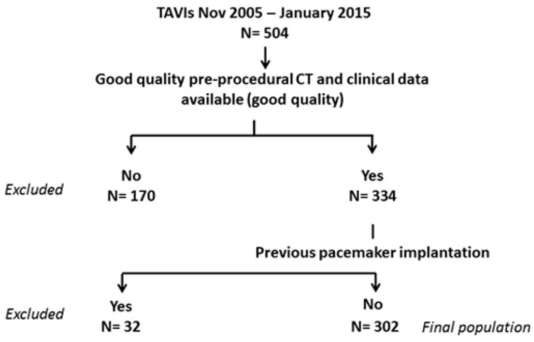

Figure 2. Study population: flow diagram.

The initial TAVR experience was with Medtronic CoreValve (Medtronic, Minneapolis, MN, USA) (MCS). In 2012 the Edwards Sapien XT (ESV-XT) (Edwards Lifesciences, Irvine, CA, USA) was added to our practice. In September 2013 the Lotus THV (Boston Scientific, Natick, Massachusetts) was introduced and followed by the Edwards Sapien S3 (Edwards Lifesciences, Irvine, CA, USA) (ESV-S3) in January 2014. The MCS and ESV-XT were considered first generation devices, conversely, Lotus and ESV-S3 second generation. Of note, given the ample literature on the association of pre-existing right bundle branch block with need for pacemaker implantation and the lower incidence of PPI with balloon-expandable ESV, patients with RBBB at baseline were preferably treated with either ESV-XT or ESV-S3 (6,13-16). THV size selection was based on MSCT derived annular dimensions.

Multi-slice computed tomography imaging

MSCT was performed with Dual Source scanners (including Somatom Definition FLASH and Force, Siemens Healthcare, Forchheim, Germany). For the assessment of the calcium load a non-contrast scan was performed in an ECG-gated, prospective, sequential (step and shoot) mode, with a tube voltage of 120 kV and slice thickness of 3mm at 1.5 mm interval. The LVOT was defined as stretching from the aortic annulus to 6 mm. on axial images.

For assessment of the LVOT a contrast enhanced ECG-triggered CT acquisition of the heart was performed. Kilovoltage and mAs settings were adapted to the individual patient. A dedicated software program (3mensio Structural Heart, PIE Medical Imaging BV, Maastricht, the Netherlands) was used for all MSCT analyses. The LVOT was defined as the area from the virtual annulus up to 6 mm into the left ventricle. The minimum LVOT dimension was identified and measured by performing a manual trace of the perimeter on double oblique reconstructions perpendicular to the LVOT axis. All the measurements were performed in end-systolic phase. Calcium load at the LVOT was semiquantitatively graded as follows: grade 0 — no calcifications (none); grade 1 — small, non-protruding calcifications (mildly calcified); grade 2 — protruding (N1 mm) (moderately calcified) or extensive (>50% of cusp sector) calcification (severely calcified). We made a distinction between non/mildly calcified and moderately/severely calcified LVOT (17). Device sizing relative to the LVOT was computed as follows: ((Normal Perimeter Device (Inflow) - LVOT perimeter) / LVOT perimeter) x 100.

Measurement of depth of implantation

To assess the depth of THV implantation (DVI), quantitative angiographic analysis was performed using CAAS 5.9 (Pie Medical, Maastricht, the Netherlands). DVI was defined as the mean of the distance from the THV inflow to the nadir of the non-coronary and left coronary cusp measured in an optimal projection where the three cusps were aligned.

Statistical analysis

Normality of the distributions was assessed using Shapiro–Wilk test. Continuous variables with normal distribution are presented as mean ± standard deviation and differences compared using the Student's

T test or ANOVA, as appropriate. Median and interquartile range was used for non-normally distributed continuous variables and differences were compared by using the Mann–Whitney U test or Kruskal–Wallis test, as appropriate. Categorical variables are presented as frequencies and differences were compared using the Pearson chi-square test.

We performed a further analysis of depth of implantation and LVOT sizing distinguishing first and second-generation devices. Additionally, we studied the relation of these 2 variables in the overall population and per device by relating tertiles of both variables. Sensitivity curves were used in order to find a cut-off value for depth of implantation

and LVOT sizing for the entire population and separately for first and second-generation devices.

To identify predictors of PPI, univariable and multivariable logistic regression was performed. Clinical and procedural relevant variables were considered for univariate analysis. Clinically relevant variables with a p-value ≤0.20 in univariate analysis entered the multivariate stage. The co-variates age and gender were included in the model

since they are well-known confounders. A maximum of 7 variables were allowed to enter the multivariable analysis given the absolute event rate of 68 in keeping with the frequency of the dependent variable y (n/10).We report crude and adjusted odds ratios together with their 95% confidence interval.

All statistical tests were two-sided, and a p-value < 0.05 was considered statistical significant. The statistical analyses were performed using SPSS software version 21.0 (SPSS INC., Chicago, IL).

RESULTS

Patient population and baseline characteristics

A total of 504 patients underwent TAVR in our center from November 2005 to January 2015. Clinical follow up and good quality MSCT were available in 334 patients; 32 patients were excluded because of a

	Total Population (n = 302)	New PPI (n = 68)	No PPI (n=234)	P-value
Age (years)	81.0 [75.0–84.0]	82.5 [77.3–86.8]	80.0 [74.0–84.0]	0.005
Gender. male (%)	154 (51.0)	38 (55.9)	116 (49.6)	0.36
Body mass index	26.2 [23.4–29.3]	25.8 [23.1–28.4]	26.3 [23.5–30.0]	0.23
Diabetes mellitus (%)	87 (28.8)	17 (25.0)	70 (29.9)	0.43
Hypertension (%)	217 (71.9)	52 (76.5)	165 (60.5)	0.34
Atrial fibrillation (%)	78 (26.1)	21 (31.3)	57 (24.6)	0.27
Prior stroke (%)	68 (22.5)	16 (23.5)	52 (22.2)	0.82
Prior MI (%)	61 (20.2)	10 (14.7)	51 (21.8)	0.20
Prior CABG (%)	67 (22.2)	14 (20.6)	53 (22.6)	0.72
Peripheral vascular disease (%)	81 (26.8)	23 (33.8)	58 (24.8)	0.14
NYHA class ≥ III (%)	226 (77.7)	51 (75.0)	175 (78.5)	0.55
Euroscore	13.0 [9.0–21.0]	13.6 [9.2–22.2]	13.0 [9.0–20.1]	0.25

Table 1. Baseline characteristics. Abbreviations: MI= myocardial infarction; NYHA = New York heart association.

permanent pacemaker at baseline resulting in an overall study sample of 302 patients (Figure 2). Baseline characteristics are summarized in Tables 1 and 2 and procedural details in Table 3. Median age was 81 (IQR 75–84) years, 51.0% were male. Median Euroscore was 13 (IQR 9–21). Two hundred and three (67.2%) patients received MCS, 38 (12.6%) ESVXT, 26 (8.6%) ESV-S3 and 35 (11.6%) Lotus. The incidence of PPI implantation within 30 days post TAVR was 22.5% (68 events): MCS 22.7%, ESV-XT 10.5%, ESV-S3 26.9% and Lotus 31.4% (p=0.17). Overall, the frequency of PPI after first generation valves was 20.7% vs.

	Total population (n = 302)	New PPI (n = 68)	No PPI (n = 234)	P-value
Electrocardiographic data				
First degree AVB (PR N 200 ms) (%)	62 (20.5)	19 (27.9)	43 (18.4)	0.086
QRS duration (ms)	105.0 [94.0–122.0]	107.0 [96.3–135.5]	103.5 [94.0–119.3]	0.088
RBBB (%)	28 (9.3)	13 (19.1)	15 (6.4)	0.001
LBBB (%)	32 (10.6)	5 (7.4)	27 (11.5)	0.32
Echocardiographic data				
LVEF (%)	50.9 ± 13.1	53.3 ± 13.6	50.2 ± 13.0	0.19
Peak aortic gradient pre (mmHg)	67.0 [54.0–85.0]	71.0 [51.8–85.0]	67.0 [55.0–85.0]	0.98
Mean aortic gradient pre (mmHg)	40.0 [31.0–52.0]	42.0 [30.0–53.5]	40.0 [31.5–52.0]	0.75
AVA pre (cm2)	0.70 [0.6–0.8]	0.70 [0.6–0.8]	0.7 [0.6–0.8]	0.88
AR ≥ grade II (%)	140 (47.6)	30 (46.9)	110 (47.8)	0.89
MR ≥ grade II (%)	164 (55.6)	37 (56.1)	127 (55.5)	0.93
MSCT data				
Annulus perimeter (mm)	78.0 [73.0–83.0]	79.0 [74.0–83.0]	77.0 [73.0–83.0]	0.26
LVOT perimeter (mm)	76.0 [70.0–82.0]	76.0 [71.2–82.8]	76.3 [70.0–81.3]	0.53
Aortic Root Agatston score	2867 [1900–4196]	2864 [1941–4612]	2904 [1883–4083]	0.52
LVOT calcium burden ≥ moderate	41 (14.2)	8 (12.3)	33 (14.7)	0.62

Table 2. Baseline electrocardiographic. echocardiographic and MSCT data. Abbreviations: AVB = atrioventricular block; RBBB = right bundle branch block; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; AVA = aortic valve area; AR = aortic regurgitation; MR = mitral regurgitation; LVOT = left ventricular out-tract.

	Total Population (n = 302)	New PPI (n = 68)	No PPI (n = 234)	P-value
Second-generation valves (%)*	61 (20.2)	18 (26.5)	43 (18.4)	0.14
Sizing annulus (%)	11.9 [4.7–16.8]	12.5 [4.7–16.8]	11.9 [4.7–16.8]	0.50
Sizing LVOT (%)	13.6 ± 11.3	15.1 ± 12.3	13.1 ± 11.0	0.20
Balloon pre-dilation (%)	250 (83.1)	54 (79.4)	196 (84.1)	0.36
Balloon post-dilation (%)	53 (17.6)	13 (19.1)	40 (17.2)	0.71
Depth of implantation (mm)	7.4 ± 3.4	8.8 ± 3.4	7.0 ± 3.3	<0.001

Table 3. Procedural characteristics. Abbreviations: LVOT = left ventricular out-tract. * Second generation valves includes ESV-S3 & Lotus valve.

29.5% after second-generation valves (p = 0.14). The most common indication for PPI was third degree atrioventricular block (61.8%). Patients requiring PPI had more first-degree AVB (27.9 vs. 18.4%, p = 0.086) and right bundle branch block (RBBB) (19.1 vs. 6.4% p = 0.001) at baseline (Table 2).

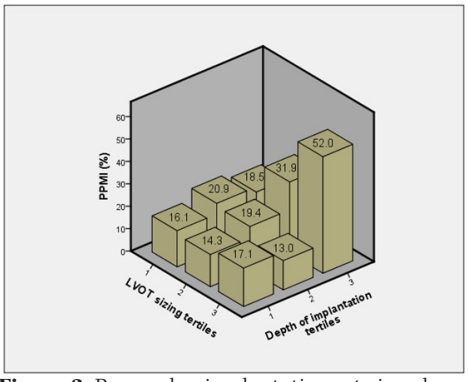

Figure 3. Pacemaker implantation rate in subgroups combining LVOT sizing and DVI tertiles for all devices.

LVOT characteristics

The LVOT perimeter was significantly smaller compared to the aortic annulus perimeter (76 mm (IQR 70–82) vs. 78 (IQR 73–83) p = 0.001). LVOT phenotype and calcium burden were not different between patients with or without need for PPI. Patients who required PPI had a deeper THV implantation into the LVOT (8.8 ± 3.4 vs. 7.0 ± 3.3 mm, p < 0.001). LVOT sizing was similar in patients with and without PPI (15.1 ± 12.3 vs. 13.1 ± 11.0%, p = 0.20). LVOT sizing for MCS, ESVXT, ESV-3 and Lotus were 16.08 ± 11.3; 9.2 ± 8.0; 6.8 ± 8.6 and 4.7±7.5% (p < 0.001). Figures 3 and 4 display the PPI rate per tertile of implantation depth and LVOT sizing overall and for each device separately.

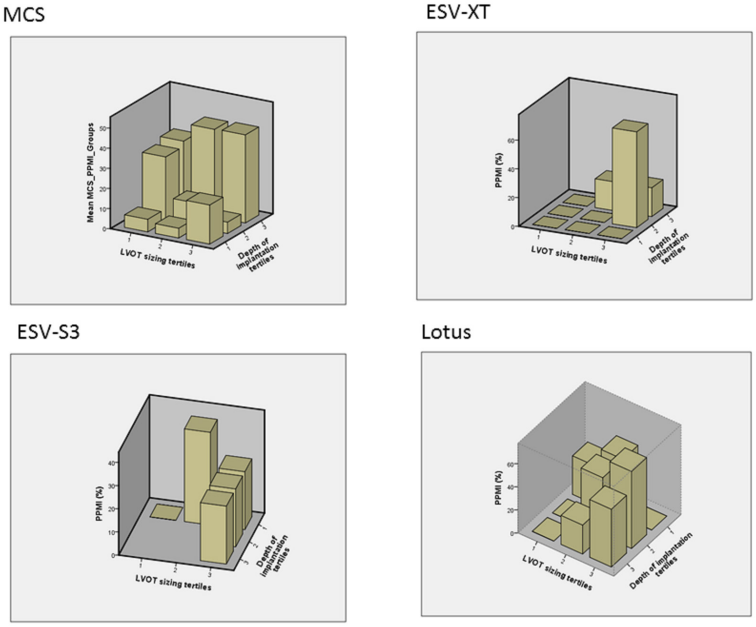

Figure 4. Pacemaker implantation rate in subgroups combining LVOT sizing and DVI tertiles per device.

	Univariate odds ratio (95% CI)	P-value	Multivariate odds ratio (95% CI)	P-value
Age	1.054 (1.012–1.099)	0.012	1.044 (0.998–1.092)	0.06
Gender. male (%)	1.289 (0.749–2.218)	0.36	1.404 (0.764–2.579)	0.28
First degree AVB	1.722 (0.922–3.216)	0.09	1.211 (0.594–2.467)	0.60
QRS duration	1.007 (0.997–1.017)	0.18		
RBBB	3.451 (1.552–7.675)	0.002	2.938 (1.243–6.945)	0.014
Second Generation valves	1.599 (0.850–3.009)	0.15	2.136 (1.006–4.532)	0.048
Depth of implantation	1.179 (1.081–1.285)	<0.001	1.196 (1.091–1.310)	<0.001
Sizing LVOT	1.016 (0.992–1.040)	0.20	1.034 (1.005–1.065)	0.022

Table 4. Univariate and multivariate logistic regression predicting new PPI. Abbreviations: AVB = atrioventricular block; RBBB = right bundle branch block; LVOT = left ventricular outflow tract.

PPI predictors

By multivariate analysis RBBB at baseline (OR 2.9 (95% CI 1.2–6.9, p = 0.014), next generation valves (OR 2.136 (95% CI 1.006–4.532), p = 0.048), depth of implantation (OR 1.196 per 1 mm increment, (95% CI 1.091–1.310), p < 0.001) and LVOT sizing (OR per 1% increment 1.034 (95% CI 1.005–1.065), p = 0.022) predicted PPI (Table 4). Patients with RBBB at baseline were preferably treated with a balloon-expandable design. Multivariate analysis excluding patients with RBBB confirmed the association between next generation valves and depth of implantation with PPI, and a trend for LVOT sizing (Supplemental Table 2). Sensitivity analysis for each THV shows 80% sensitivity for the association LVOT sizing and PPI (Figure 5) at 10% oversizing with MCS, 9% with ESV-XT, 3%with ESV-S3 and 2%with Lotus valve. As for depth of implantation, 80% sensitivity was obtained with a depth of 6.3 mm for both MCS and ESV-XT, 7.0 mm for the ESV-S3 and 6.7 mm for the Lotus valve (Figure 6).

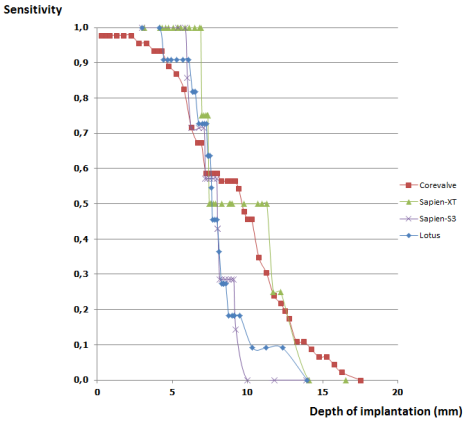

Figure. 5. Sensitivity curve per device for the relation LVOT sizing and PPI.

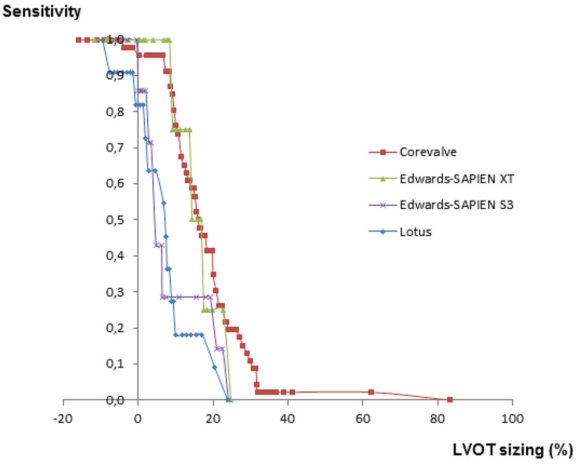

Figure. 6. Sensitivity curve per device for the relation PPI and depth of implantation.

DISCUSSION

The key findings of our observational study can be summarized as follows. 1) LVOT oversizing but not LVOT calcium burden is associated with PPI. 2) Depth of implantation strengthens the association of sizing with PPI. 3) The degree of LVOT oversizing triggering PPI is less for next generation THVs.

Need for PPI after TAVR reportedly varies between 2 and 51% and is consistently higher with the self-expanding MCS as compared to the balloon expandable Edwards THV (6). In the randomized CHOICE trial the 30-day PPI rate was 17% for the ESV-XT vs. 37.6% for the MCS (p = 0.001) (18). In the PRAGMATIC initiative the difference was 6% for ESV-XT vs. 22.5% for MCS, p < 0.001) (19). A recent meta-analysis also confirmed the higher need for PPI with MCS (28% vs. 6%) (6). The higher need for PPI with MCS may be related to the self-expanding design that may be prone to deeper implants and delayed tissue injury. In our study 4 different THVs were used, yet we did not detect significantly different PPI rates among these THV designs. This may be explained by selection bias and our policy to treat patients with RBBB at baseline preferably with balloon-expandable devices given the compelling association of RBBB with PPI and the higher need for PPI with MCS in previous studies (6). Interestingly the composite of next generation

THVs (ESV-S3 and Lotus) was associated with more PPI (2.136 (95% CI 1.006–4.532) p = 0.048).

Traditional risk factors for PPI post TAVR are RBBB and depth of THV implantation. This reality reflects the anatomic vicinity of the atrioventricular conduction system and the native aortic valve. Indeed, the AV node and its extension the bundle of His is adjacent to the membranous interventricular septum and particularly the left bundle is close to the base of the interleaflet triangle between the right and non-coronary leaflets. It is conceivable that a device deployed in the LVOT and thus pressing on this conduction system may induce trauma to the left bundle and even more so if the interface is larger in association with a deeper implant eventually resulting in high degree AV block a fortiori when pre-existing RBBB exists (8,20). In our analysis 1st degree AV block trended to be associated and RBBB highly correlated with need for PPI. These findings underscore a recent meta-analysis including 11,210 patients that demonstrated strong correlations between 1st degree AV block (OR 1.52) and RBBB (OR 2.89) with need for PPI (6). Interestingly, we also detected a close to significant correlation between age and need for PPI. This may feed the hypothesis that the conduction system in younger patients could be less vulnerable to TAVR induced trauma. Depth of implantation has previously been associated with need for PPI (21,22). In our study mean depth of implantation was similar for all THVs and was associated with more PPI. As for the LVOT phenotype and need for PPI, calcium was no factor whereas relative LVOT oversizing was, especially when adjusted for depth of THV implantation. Currently, most sizing algorithms specifically focus on annular dimensions for THV size selection. Yet the anatomical dimensions significantly taper down moving into the LVOT as was shown in our study. Baan et al. demonstrated that a smaller left ventricular outflow tract diameter by 2D echocardiography was a predictor for PPI with MCS (23). A PARTNER sub-study revealed that the ESV prosthesis to LVOT ratio assessed by 2D echocardiography, correlated with PPI (7). Typically first generation THVs require 10 to 20% oversizing relative to the aortic annulus. The degree of LVOT oversizing that predicts PPI seems considerably less and even smaller for second-generation THVs vs. first generation THVs. Interestingly, in our study the impact of LVOT oversizing seemed greater with deeper implants. Deeper implants would result in a larger interface between the THV and the underlying conduction system and therefore a higher likelihood of traumatic compression. Furthermore, additional sealing skirts with ESV-S3 and Lotus may minimize paravalvular regurgitation at the expense of more compression on surrounding tissue (Figure 1) (24). Our data suggest that patients with RBBB at baseline are at risk for PPI after TAVR regardless of the selected THV design. Yet, efforts to reduce depth of THV implantation and refined sizing algorithms with specific attention to the LVOT dimensions to avoid excessive sizing at the LVOT level may reduce PPI rates particularly with second-generation THVs. Indeed more attention to the LVOT may not only reduce the risk for aortic root rupture but also need for PPI (25).

Limitations

This is a single center observational study using 4 different THV designs with unequal patient distribution. Also patients with RBBB at baseline were preferably treated with balloon expandable THVs, which may have resulted in higher PPI rate. The number of patients per THV was too small to demonstrate significant inter-device differences, yet our observations in terms of LVOT oversizing and depth of implantation are clinically relevant and require confirmation in adequately powered studies.

CONCLUSIONS

LVOT sizing is associated with need for permanent pacemaker implantation after TAVR, even more so with deeper THV implants and second generation devices (ESV-S3 and Lotus). Sizing algorithms should focus more on LVOT dimensions to reduce PPI.

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SUPPLEMENTAL MATERIAL

	Total Population (n = 302)	MCS (n= 202)	ESV-XT (n=38)	ESV-S3 (n=26)	Lotus (n=35)	P-value
Age (years.)	81.0 [75.0 – 84.0]	81.0 [76.0-85.0]	75.5 [72.0-81.3]	83.5 [79.0-85.8]	81.0 [75.0-85.0]	0.002
Gender. male (%)	154 (51.0)	105 (51.7)	20 (52.6)	15 (57.7)	14 (40.0)	0.52
Body mass index	26.2 [23.4 – 29.3]	26.0 [23.4-28.5]	26.2 [21.9-30.7]	27.7 [25.0-31.8]	26.3 [22.9-30.0]	0.21
Diabetes Mellitus (%)	87 (28.8)	56 (27.6)	10 (26.3)	9 (34.6)	12 (34.3)	0.75
Hypertension (%)	217 (71.9)	135 (66.5)	30 (78.9)	22 (84.6)	30 (85.7)	0.026
Atrial fibrillation (%)	78 (26.1)	51 (25.2)	7 (18.4)	7 (26.9)	13 (39.4)	0.23
Prior Stroke (%)	68 (22.5)	48 (23.6)	6 (15.8)	4 (15.4)	10 (28.6)	0.45
Prior MI (%)	61 (20.2)	37 (18.2)	12 (31.6)	5 (19.2)	7 (20.0)	0.31
Prior CABG (%)	67 (22.2)	48 (23.6)	6 (15.8)	6 (23.1)	7 (20.0)	0.74
Peripheral vascular disease (%)	81 (26.8)	46 (22.7)	15 (39.5)	9 (34.6)	11 (31.4)	0.11
NYHA class ≥ III (%)	226 (77.7)	154 (77.8)	27 (73.0)	22 (84.6)	23 (76.7)	0.75
Euroscore	13.0 [9.0 -21.0]	13.4 [9.4-21.3]	9.8 [6.9-19.3]	14.0 [7.5-22.2]	12.1 [9.2-20.2]	0.12
First degree AVB (%)	62 (20.5)	46 (22.7)	6 (15.8)	3 (11.5)	7 (20.0)	0.50
QRS duration (ms)	105.0 [94.0 -122.0]	106.0 [95.8-120.0]	100.5 [89.0-143.5]	105.0 [98.5-119.0]	101.0 [94.0-122.0]	0.83
RBBB (%)	28 (9.3)	12 (5.9)	7 (18.4)	6 (23.1)	3 (8.6)	0.006
LBBB (%)	32 (10.6)	26 (12.8)	3 (7.9)	0 (0.0)	3 (8.6)	0.21
LVEF (%)	50.9 ± 13.1	49.7 ± 13.3	48.5 ± 12.3	53.1 ± 14.2	56.7 ± 10.1	0.079
Peak aortic gradient pre (mmHg)	67.0 [54.0 -85.0]	71.0 [54.0-85.8]	71.5 [51.8-85.0]	64.0 [58.8-82.3]	65.5 [52.8-79.3]	0.70
Mean aortic gradient pre (mmHg)	40.0 [31.0 -52.0]	41.0 [31.3-52.0]	41.0 [30.0-56.1]	39.5 [31.0-52.5]	37.5 [30.0-46.5]	0.75
AVA pre (cm2)	0.70 [0.6 -0.8]	0.7 [0.5 -0.8]	0.8 [0.7-0.9]	0.7 [0.6-0.9]	0.7 [0.6-0.9]	0.082
AR ≥ grade II (%)	140 (47.6)	86 (42.8)	26 (68.4)	11 (47.8)	17 (53.1)	0.030
MR ≥ grade II (%)	164 (55.6)	97 (48.0)	24 (64.9)	18 (75.0)	25 (78.1)	0.001
Annulus perimeter (mm)	78.0 [73.0 -83.0]	78.0 [73.0-83.8]	77.0 [72.8-82.0]	79.0 [74.8-83.8]	76.0 [72.0-82.5]	0.55
LVOT perimeter (mm)	76.0 [70.0 -82.0]	77.0 [70.0 -83.0]	74.5 [70.0-80.0]	75.3 [71.0-82.0]	73.9 [71.0-79.0]	0.52
Agatston score Aortic Root	2867 [1900 -4196]	2934 [1899-4340]	2719 [1925-4841]	3174 [2194 -4553]	2649 [1858-3332]	0.37
LVOT calcium burden ≥ moderate	41 (14.2)	31 (15.9)	5 (13.9)	2 (8.3)	3 (8.8)	0.58
Sizing annulus (%)	11.9 [4.7 – 16.8]	13.9 [9.8-19.5]	4.7 [1.6-8.9]	3.5 [0.7 -6.9]	1.0 [-0.2-3.1]	<0.001
Sizing LVOT (%)	13.6 ± 11.3	16.8 ± 11.3	9.2 ± 8.0	6.9 ± 8.6	4.7 ± 7.5	<0.001

Balloon pre-dilation (%)	250 (83.1)	188 (93.1)	37 (97.4)	16 (61.5)	9 (25.7)	<0.001
Balloon post-dilation (%)	53 (17.6)	40 (19.8)	10 (26.3)	3 (11.5)	0 (0.0)	0.013
Depth of implantation (mm)	7.4 ± 3.4	7.3 ± 3.8	7.7 ± 2.5	7.6 ± 2.1	7.6 ± 2.0	0.90

Supplemental table 1. Baseline clinical and procedural characteristics per device. Abbreviations: AVA = aortic valve area; AR = aortic regurgitation; AVB = atrioventricular block; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; LVOT = left ventricular outflow tract; MI = myocardial infarction; MR = mitral regurgitation; NYHA = New York heart association; RBBB = right bundle branch block.

	Univariate odds ratio (95% CI)	**P-value**	**Multivariate odds ratio (95% CI)**	**P-value**
Age	1.041 [0.997 – 1.087]	0.067	1.034 [0.987 – 1.084]	0.16
Gender. Male (%)	1.189 [0.658 – 2.149]	0.57	1.327 [0.698 – 2.523]	0.39
First degree AVB	1.576 [0.784 – 3.169]	0.20	1.301 [0.605 – 2.799]	0.50
QRS duration	0.997 [0.985 – 1.011]	0.71		
Second Generation valves	1.845 [0.925 – 3.680]	0.082	2.394 [1.083 – 5.293]	0.031
Depth of implantation	1.176 [1.070 – 1.293]	0.001	1.185 [1.075 – 1.307]	0.001
Sizing LVOT	1.013 [0.985 – 1.042]	0.371	1.029 [0.995 – 1.064]	0.096

Supplemental table 2. Univariate and multivariate logistic regression predicting new PPI. excluding patients with RBBB at baseline. Abbreviations: AVB = atrioventricular block; RBBB = right bundle branch block; LVOT = left ventricular outflow tract.

Part II
Vascular complications

CHAPTER VI

The MANTA vascular closure device a novel device for large-bore vessel closure

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Catheter-based therapies may offer a less invasive alternative to conventional surgery for a wide array of cardiovascular diseases. These percutaneous interventions often require large-bore catheters, and vascular access management may be challenging. Suture-based closure devices can be used for arteriotomy closure. Transcatheter aortic valve replacement (TAVR) involves such large-bore arteriotomy closure. Despite smaller device profiles and growing experience with TAVR, the reported incidence of vascular complications still varies between 1% and 13% (1-3). Up to two-thirds of major vascular complications after TAVR are due to failed arteriotomy closure (4).

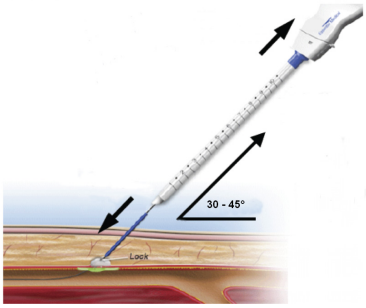

Figure 1. MANTA concept. A bovine collagen pad in gray seals the arteriotomy from the outside of the vessel and is connected with the endoluminal bioresorbable toggle through a suture that is closed by a stainless steel suture lock.

The percutaneous MANTA vascular closure device (VCD) (Essential Medical Inc., Malvern, Pennsylvania) is a novel collagen-based technology dedicated to the closure of large bore arteriotomies. The MANTA VCD contains an 8-F puncture location dilator, a dedicated sheath, a closure unit, and a delivery system. The closure unit consists of a resorbable polymer (poly-lactic-co-glycolic acid) intra-arterial toggle, an extravascular hemostatic bovine collagen pad, a connecting nonresorbable polyester suture, and a stainless steel suture lock, illustrated in Figure 1. This closure unit is attached to the delivery system that contains a carrier/release tube and a device handle with a tension gauge. Both the puncture location dilator and the MANTA sheath have centimeter markers on the respective surfaces. MANTA comes in 14-F and 18-F sizes for closing punctures of 10 to 14 F and 15 to 22 F, respectively. Use of the MANTA VCD precludes a pre-closure technique. After common femoral artery access is obtained with a 6-F sheath, this sheath is exchanged for the 8-F puncture location dilator to determine the distance of the subcutaneous track from skin level to the endoluminal arterial space. The planned cardiovascular intervention is then executed by upscaling the access sheath. Thereafter the procedural sheath is exchanged for the dedicated MANTA sheath to receive the MANTA closure unit. The MANTA sheath closure unit assembly is withdrawn up to the predetermined deployment level. The toggle is released and the assembly is withdrawn from the patient. Pulling force can be monitored by the color code of the tension gauge. The blue tamper tube emerges and is advanced along the suture line to secure the stainless steel lock onto the vessel and further compact the collagen pad. The suture is cut above the tamper and at skin level. It takes 6 months for the MANTA components to resorb so that only the polymer suture and stainless steel suture lock remain at the access site.

In our initial MANTA experience in 10 consecutive patients undergoing TAVR (n = 8), balloon aortic valvuloplasty (n = 1), and high-risk percutaneous intervention with a 14-F circulatory support device (n = 1), sheath sizes varied from 14 to 22 F. MANTA access closure was successful in all patients. Hemostasis was obtained within 22 ± 20 s after starting MANTA deployment. A patent artery was angiographically confirmed in all cases. There were neither significant bleeding events nor vascular complications at the access site closed by MANTA. Our initial experience supports further study to determine if use of the MANTA VCD could reduce access-site complications with large-bore cardiovascular interventions. The CE-mark study (NCT02521948) to evaluate the safety and performance of the MANTA VCD has completed enrollment, and results will be presented in 2016.

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CHAPTER VII

MANTA, a novel plug-based vascular closure device for large bore arteriotomies

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ABSTRACT

Catheter-based interventions have become a less invasive alternative to conventional surgical techniques for a wide array of cardiovascular diseases but often create large arteriotomies. A completely percutaneous technique is attractive as it may reduce the overall complication rate and procedure time. Currently, large bore arteriotomy closure relies on suture-based techniques. Access-site complications are not uncommon and often seem related to closure device failure. The MANTA VCD is a novel collagen-based closure device that specifically targets arteriotomies between 10 and 22 Fr. This technical report discusses the MANTA design concept, practical instructions for use and preliminary clinical experience.

Introduction

For a wide array of cardiovascular diseases less invasive catheter-based therapies have become available as an alternative to conventional surgery. Achieving large bore catheter access and vascular access management may be challenging. For large arteriotomies (>12 Fr) suture-based percutaneous closure devices such as Prostar XL (Abbott Vascular, Santa Clara, CA, USA) or Perclose ProGlide (Abbott Vascular) are an established technique, yet major vascular complications are relatively common (1).

Balloon aortic valvuloplasty (BAV) – with sheath sizes of 10 to 13 Fr – is associated with major vascular complications in 7% of cases (2), and with transcatheter aortic valve implantation (TAVI) this rate goes up to 12% (3). The ClOsure device iN TRansfemoral aOrtic vaLve implantation (CONTROL) multicentre study, comparing Prostar with ProGlide, showed more major vascular complications with Prostar (4). Two thirds of major vascular complications after TAVI result from failed arteriotomy closure (5).

Over time, the rate of vascular complications has gradually declined due to growing experience, improved access technique with fluoroscopic or ultrasound guidance and design modifications with smaller profile devices (6,7); yet, access-site complications and bleedings are still fairly common and associated with mortality (8). Precautionary crossover balloon occlusion may facilitate suture-based closure but requires an additional femoral or radial arterial access and may increase overall procedural costs (9).

The percutaneous MANTA Vascular Closure Device (VCD) (Essential Medical Inc., Malvern, PA, USA) is a novel collagen-based technology for closure of large bore arteriotomies. This technical report describes the MANTA design concept, practical instructions for use and preliminary clinical experience.

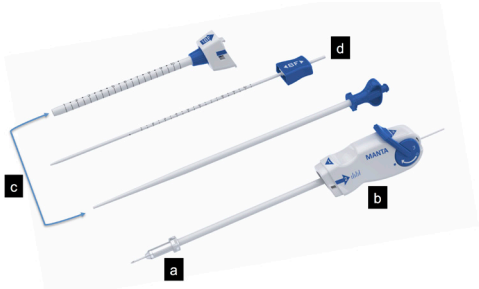

Figure 1. MANTA closure device. Shown are closure unit (A), delivery system (B), dedicated sheath with introducer (C), and 8 Fr puncture location dilator (D). The sheath and location dilator have centimetre markers.

MANTA design

The MANTA VCD has a closure unit, a delivery system and a dedicated sheath with introducer. There is also a separate 8 Fr puncture location dilator (Figure 1). The puncture location dilator and the MANTA sheath both have a visible metric ruler for assessing the adequate depth. The closure unit comprises the following components: a resorbable polymer (poly-lactic-co-glycolic acid) intra-arterial toggle, an extravascular haemostatic bovine collagen pad, a connecting non-resorbable polyester suture, and a stainless steel suture lock (Figure 2). The delivery system has a tube containing the closure unit and a device handle with a tension gauge to release the closure unit from the tube. The MANTA system comes in a 14 Fr or 18 Fr size. The 14 Fr MANTA VCD is indicated for closing punctures of 10 to 14 Fr, the 18 Fr MANTA VCD for punctures of 15 to 22 Fr.

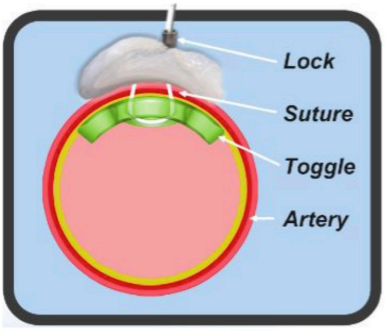

Figure 2. MANTA concept.
A bovine collagen pad (in grey) seals the arteriotomy from the outside of the vessel and is connected with the endoluminal bioresorbable toggle through a suture that is closed by a stainless steel suture lock.

Technique

Ultrasound or fluoroscopy guidance may help to achieve a median anterior vessel entry. Angiography should confirm access quality. Pre-closure is not necessary with the MANTA system. Figure 3 and Supplemental Figure 1 illustrate the procedural steps with MANTA closure. After a 0.035" guidewire and 6 Fr sheath are introduced into the common femoral artery, the sheath is exchanged for the 8 Fr puncture location dilator to measure the length of the subcutaneous track from the skin to the endovascular lumen. Pulsatile blood emerges when the dilator tip is in the arterial vessel. The operator pulls back the dilator until the blood flow ceases and the depth of the vessel lumen can be read from the metric ruler. Empirically 2 cm is added to assure endoluminal deployment of the toggle during the actual MANTA delivery. The arterial access is then up-scaled to the proper sheath size to perform the index procedure. At the end of the index procedure, significant subcutaneous blood collection should be excluded before using the MANTA VCD because significant haematoma could alter the puncture depth relative to the state at baseline. The procedural sheath is exchanged over a 0.035" guidewire for the dedicated MANTA sheath.

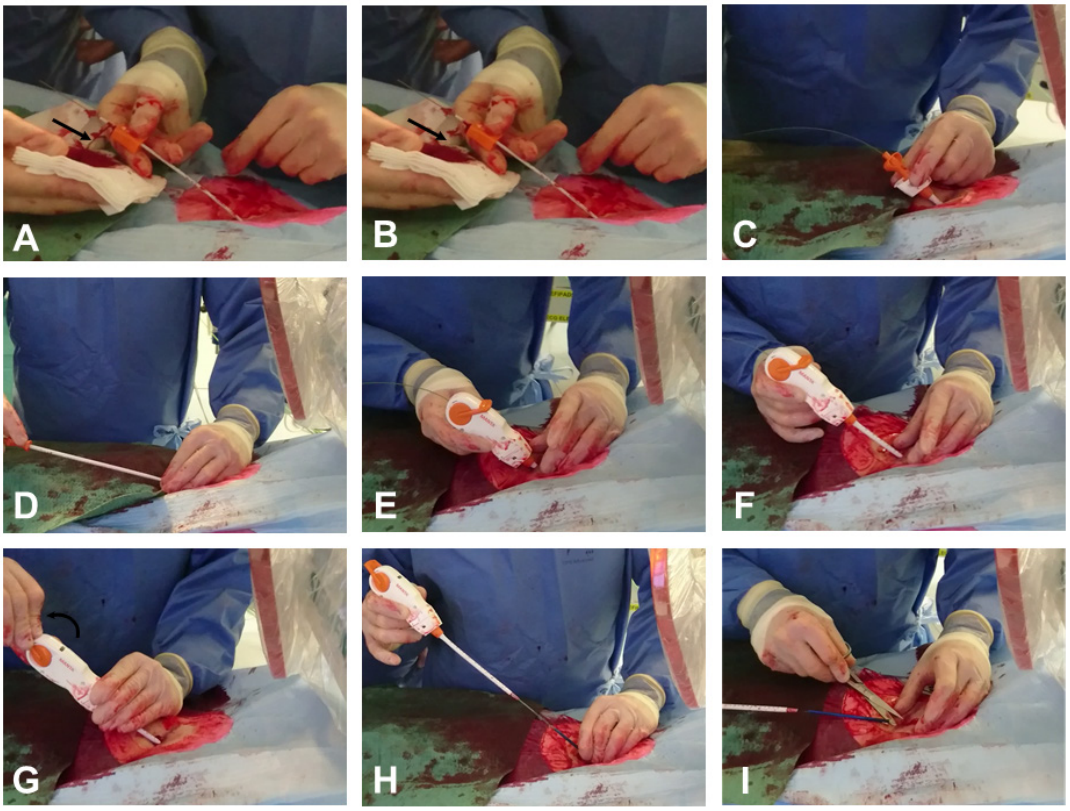

Figure 3. MANTA closure in real practice. A) Puncture depth estimation with the 8 Fr puncture location dilator. Note (pulsatile) blood exiting on the side (black arrow). B) The location dilator is re-advanced and blood ceases (black arrow). C) The MANTA sheath is introduced over a 0.035" guidewire. D) The sheath introducer is removed. E) The MANTA closure unit is advanced over the wire into the sheath. F) The MANTA sheath closure unit assembly is slowly withdrawn at a 45° angle with the right hand while providing slight left hand counter push to the skin level to avoid skin tenting. G) The lever is rotated (orange arrow) to release the toggle. H) The assembly is slowly withdrawn from the patient along the angle of the initial puncture. Pulling force can be monitored by the colour code of the tension gauge and the tamper tube is advanced down along the suture line. I) The suture is cut above the tamper and at skin level.

The sheath introducer is removed and the MANTA closure unit is advanced over the wire into the sheath until the MANTA delivery hub snaps the sheath hub and a clicking sound will be heard. The MANTA sheath closure unit assembly is then slowly withdrawn at a 45° angle with the right hand while providing slight left hand counter push to the skin level to avoid skin tenting. At the predetermined deployment level, the toggle is released by rotating the lever of the MANTA delivery handle in a clockwise direction. The assembly is then slowly and gently withdrawn from the patient. Pulling force can be monitored by a colour code. When excessive force is applied the colour code will switch from green to red, accompanied by an audible "click". As the MANTA sheath clears the skin layer a blue tamper tube emerges from the deployment tube. Digital left hand pressure around the puncture site is released to advance the tamper tube down along the suture line and secure the stainless steel lock onto the vessel to compact the collagen pad further. The black suture marker becomes visible to indicate full compaction of the collagen. At this point, the arterial wall is sandwiched between toggle and collagen. Tension on the assembly is released and the tamper is slid up the suture line out of the puncture tract. When haemostasis is confirmed, the guidewire is removed. If needed, a final tamp with tension on the handle and monitored pressure on the tamper (green colour at tension gauge) can be performed to ensure complete haemostasis. The suture is cut above the blue tamper and at skin level.

The MANTA components will resorb in six months. In the event that the patient requires re-access within six months from MANTA closure, X-ray should be used to identify the radiopaque lock, and the common femoral artery should be punctured at least 2.5 cm from the present MANTA device.

MANTA closure should be used with caution at puncture sites: 1) in the proximity (<1 cm) of large bifurcations, 2) with significant atherosclerotic disease or circumferential calcifications, or 3) with non-central vessel entry.

Initial Rotterdam experience

MANTA closure was applied in 10 consecutive patients undergoing various large bore catheter interventions, including TAVI (n=8), BAV (n=1) and high-risk percutaneous intervention with a 14 Fr circulatory support device (n=1). All patients underwent pre-procedural planning by MSCT and/or ultrasound plus ad hoc angiography to assess the iliofemoral arterial tree in terms of size, atherosclerotic disease, calcium distribution

		N=10
Age in years (mean±SD)		79±6
Male gender (n)		8
BMI in kg/m^2 (mean±SD)		27±4
Glomerular filtration rate in ml/min (mean±SD)		55±26
Stroke (n)		3
Atrial fibrillation (n)		2
Pacemaker (n)		3
Bundle branch block (n)	No	4
	LBBB	1
	RBBB	2
Prior myocardial infarction (n)		3
Prior CABG (n)		2
Prior PCI (n)		2
Diabetes mellitus (n)		4
Hypertension (n)		7
Peripheral vascular disease (n)		3
COPD (n)		2
New York Heart Association Class (n)	II	4
	III	3
	IV	3

Table 1. Baseline characteristics. Abbreviations: BMI = body mass index; CABG = coronary artery bypass grafting; LBBB = left bundle branch block; PCI = percutaneous coronary intervention; RBBB = right bundle branch block

and tortuosity. Baseline patient characteristics are displayed in Table 1. Mean age was 79±6 years, and eight of the 10 patients were male. Procedural characteristics are shown in Table 2. Sheath size closed with the MANTA device varied from outer diameter 14 Fr to 22 Fr, including the self-expanding eSheath technology (Edwards Lifesciences, Irvine, CA, USA) in five patients. The 14 Fr and 18 Fr MANTA were used in three and seven patients respectively. MANTA access closure was successful in all patients. Time from toggle release (i.e., start of device deployment) to haemostasis was 22±20 seconds. Angiography confirmed a patent artery in all cases. There were no relevant bleeding or vascular complications after MANTA closure. One patient experienced a major vascular complication due to laceration of the inferior epigastric artery in the contralateral access site that was not related to the MANTA VCD.

		N=10
Procedure sheath size (n)	14 Fr	3
	14 Fr – eSheath	2
	16 Fr – eSheath	3
	20 Fr	2
Procedure type (n)	TAVI	8
	BAV	1
	Percutaneous heart pump	1
Valve type, if TAVI was performed (n)	Edwards SAPIEN 3 29 mm	3
	Edwards SAPIEN 3 26 mm	2
	Boston Scientific Lotus 27 mm	2
	Medtronic Evolut R 26 mm	1
MANTA sheath size (n)	14 Fr	3
	18 Fr	7
Bleeding <24 hr (n)	No bleeding	9
	Minor bleeding	0
	Major bleeding	0
	Life-threatening bleeding	1*
Bleeding >24 hr (n)	No bleeding	10
Vascular complication (n)	No vascular complications	9
	Minor	0
	Major	1*
Percutaneous closure device failure (n)		0
Unplanned closure technique (n)		0
Time to haemostasis in seconds (mean±SD)		22±20
Patent artery after deployment of MANTA VCD (n)		10
Manual pressure needed to achieve haemostasis (n)		0

Table 2. Procedure characteristics. *One patient experienced a life-threatening bleeding from the contralateral inferior epigastric artery. Abbreviations: BAV = balloon aortic valvuloplasty; TAVI = transcatheter aortic valve implantation

Conclusion

Early clinical experience is promising but needs confirmation in larger clinical trials. Results from the CE-mark study (NCT 02521948) to evaluate the safety and performance of MANTA VCD are awaited in 2016.

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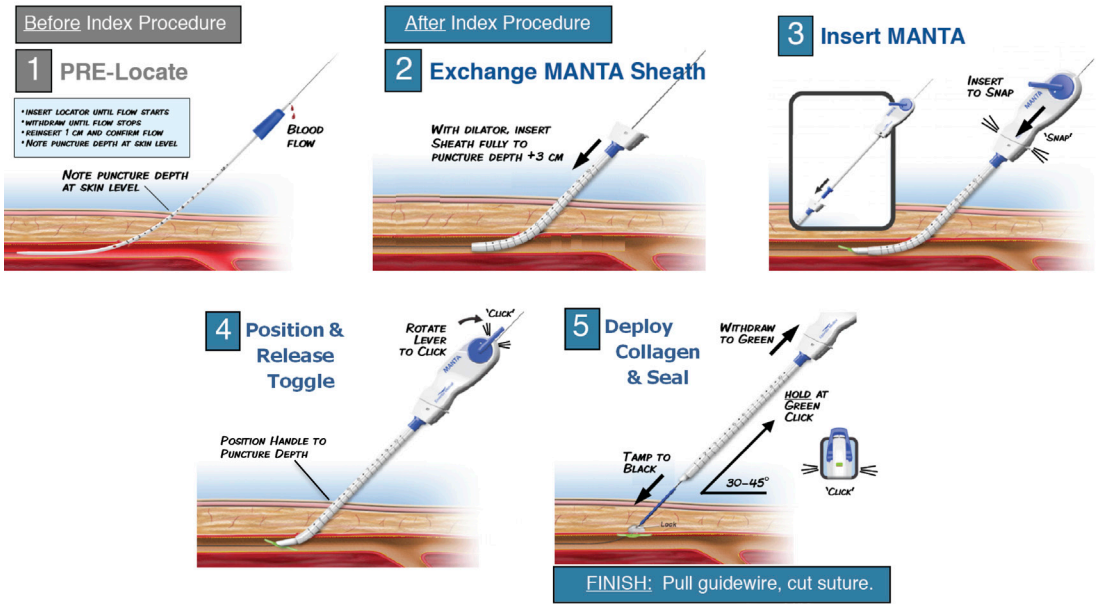
9. Genereux P, Kodali S, Leon MB et al. Clinical outcomes using a new crossover balloon occlusion technique for percutaneous closure after transfemoral aortic valve implantation. JACC Cardiovascular interventions 2011;4:861-7.

SUPPLEMENTAL MATERIAL



Supplemental figure 1. Typical MANTA closure.

CHAPTER VIII

Percutaneous plug-based arteriotomy closure device for large-bore access a multicenter prospective study

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ABSTRACT

Objectives

The authors sought to study the safety and efficacy of the MANTA Vascular Closure Device (VCD), a novel collagen-based technology dedicated to closure of large-bore arteriotomies.

Background

Novel transfemoral therapeutic interventions requiring large-bore catheters have become valid minimally invasive options but have inherent access management challenges. To date, no dedicated vascular closure devices exist for large arteriotomies.

Methods

A prospective, single-arm clinical investigation enrolling patients who underwent elective percutaneous interventions with large-bore catheters and planned percutaneous arteriotomy closure in 3 European institutions.

Results

A total of 50 patients with a mean age of 79.5 ± 8.3 years underwent high-risk percutaneous coronary intervention, balloon aortic valvuloplasty, or transcatheter aortic valve replacement with large-bore catheters sized 12-F to 19-F. MANTA closure was performed by 9 different operators. The 14-F MANTA VCD was deployed in one-third of the overall cohort (16 of 50, 32%), and the 18-F MANTA VCD in the remainder. The MANTA VCD was deployed successfully in all patients. The mean time to hemostasis was 2 min, 23 s. One patient had a major vascular and major bleeding complication with prolonged femoral bleeding that was successfully treated with a covered stent and eventual surgical repair. There were no other access site–related complications.

Conclusions

This first multicenter experience demonstrates rapid and reliable hemostasis and low complication rates with the use of the plug-based MANTA VCD for large-bore arteriotomy closure.

INTRODUCTION

The advent of endovascular aneurysm repair, transcatheter aortic valve replacement (TAVR), and mechanical circulatory support has offered new, minimally invasive therapeutic options that are rapidly becoming standard of care. These percutaneous transfemoral interventions require large-bore catheters and have created challenges for femoral arterial access management. Current approaches include surgical cut-down with arterial puncture under direct vision, and suture-based "pre-closure." Surgical cut-down is associated with longer procedural time, increased patient discomfort, deeper anesthesia, risk of wound complications including infection, and slower ambulation. The pre-closure technique overcomes many of the disadvantages of surgical cut-down but can be technically demanding, time consuming, and associated with a significant failure rate. Recent randomized TAVR trials have reported major vascular complications in 6% to 8% (1,2). Furthermore, a study on the 2 suture-based closure techniques for management of TAVR access reported a 20% vascular complication rate despite being used by experienced operators (3). Currently, the majority of access site complications result from failed arteriotomy closure (4).

The percutaneous MANTA Vascular Closure Device (VCD) (Essential Medical Inc., Malvern, Pennsylvania) is a novel collagen-based technology dedicated to closure of large-bore arteriotomies (5). The MANTA VCD underwent prospective multicenter evaluation for Conformité Européenne (CE) mark approval in the first detailed report of outcomes achieved with a dedicated large-bore vascular closure device.

METHODS

This prospective, multicenter, non-blinded, single-arm clinical investigation enrolled 50 patients in 3 European institutions. Eligible patients underwent elective percutaneous interventions with large-bore catheters sizes 12-F to 19-F (sheath outer diameter (OD) profile of 16-F to 24.5-F) and planned percutaneous arteriotomy closure. All patients were discussed in a multidisciplinary heart team including interventional cardiologists and cardiac/vascular surgeons. Key exclusion criteria were: 1) arterial puncture outside of the common femoral artery; 2) common femoral artery size inappropriate for the selected sheath size; 3) complicated femoral access, including excessive hematoma surrounding the puncture site, arteriovenous fistula, and posterior wall puncture; 4) renal insufficiency defined by a serum creatinine >2.5 mg/dl; and 5) inability to ambulate at baseline. Patients provided written informed consent before enrolment. Operators were first-time users of the MANTA VCD, and their training included a detailed device description and bench-top training on a dry plastic model. The study design was approved by each institutional review board and was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice principles, and the International Organization for Standardization of medical devices for human subjects (ISO 14155:2011). The study was registered as NCT02521948 (Clinical Study to Evaluate the Safety and Performance of MANTA Vascular Closure Device).

Device description

A detailed description of the MANTA VCD and its mode of operations has been previously described in detail (5). In brief, the MANTA VCD consists of an implantable closure unit and a delivery system. The delivery system comprises a device handle, a carrier/release tube, a custom introducer and device sheath,

and an 8-F puncture location dilator (Figure 1). The location dilator and device sheath have centimeter markers. The closure unit consists of an intra-arterial bioresorbable polymer (poly-lactic-co-glycolic acid) toggle, an extra-vascular hemostatic bovine collagen pad, a connecting non-resorbable polyester suture, and a stainless steel suture lock. Hemostasis is achieved primarily by the mechanical means of the toggle-arteriotomy-collagen sandwich, which is supplemented by the coagulation-inducing properties of the collagen. With the exception of the perivascular stainless steel lock (1.6 ± 2.9 mm) and the polyester suture that ties the collagen, toggle, and lock together, all MANTA composites are resorbed within 6 months. In the event the patient requires re-access within 6 months from MANTA closure, fluoroscopy should be used to identify the radio-opaque lock, and the common femoral artery should be punctured at least 2.5 cm away from the present MANTA device.

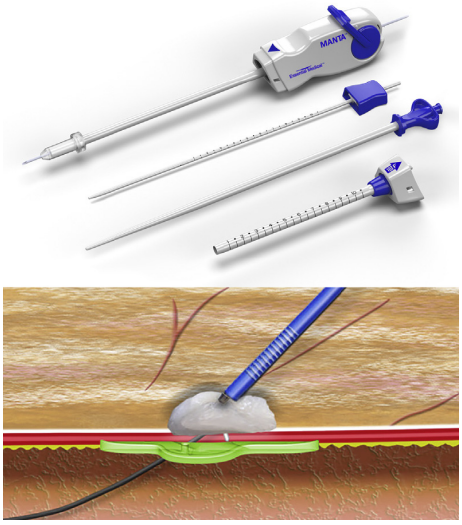

Figure 1. MANTA Vascular Closure Device. (Upper panel: from top to bottom) MANTA device with closure unit, 8-F puncture locator, introducer, and sheath. (Lower panel) Schematic representation of arteriotomy closure with MANTA toggle and plug.

Procedure planning and execution

Computed tomography (CT) angiography of the iliofemoral arterial tree was recommended for all patients and was typically available for all TAVR patients. Ultrasound assessment of the common femoral arteries before the procedure, pre-discharge, and at 30 days and 60 days after the procedure, as well as selective angiography following arterial access with a 6-F sheath and after MANTA access closure attempt, were mandatory per protocol. After successful and uncomplicated access confirmation, the initial sheath was exchanged for the MANTA puncture location dilator to measure the distance from the arteriotomy to the skin level. The access was then up-scaled per planned procedural requirements. At the end of the percutaneous intervention, the large-bore access sheath was exchanged for the dedicated MANTA sheath. The MANTA device is inserted into the dedicated sheath and positioned according to puncture distance. Once the toggle is released, the seal is achieved through familiar tamping procedure and confirmed with the included tension gage. Deployment takes 1 to 2 min. The 14-F and 18-F MANTA VCD accommodate 10-F to 14-F (OD profile 14-F to 18-F) and 14-F to 19-F (OD profile 18-F to 24.5-F) access sheath sizes, respectively. All interventions were performed under anticoagulation with heparin, aiming for an activated clotting time between 250 and 300 s. At the time of MANTA VCD deployment, the activated clotting time needed to be below 250 s with a systolic blood pressure <180 mm Hg. Heparin reversal with protamine was at the operator's discretion.

Safety and effectiveness

The primary means of evaluating safety was occurrence of any access site–related vascular injury, as well as major and life threatening/disabling bleeding complications according to the most recent Valve Aca-

demic Research Consortium (VARC) definitions (6). The primary performance endpoint was hemostasis success, defined as hemostasis at the puncture site within 10 min of removing the MANTA sheath without need for manual or mechanical compression and without later re-bleeding. Secondary performance endpoints included time to hemostasis (TTH). TTH was defined as the elapsed time between MANTA deployment (withdrawal of sheath from artery) and the first observed and confirmed arterial hemostasis (no or minimal subcutaneous oozing and the absence of expanding or developing hematoma). All patients returned for a clinical and ultrasound follow-up including ankle brachial indices and a plain x-ray of the femoral access site. Demographic, procedural, and endpoint data were entered in electronic case report forms. An independent clinical research organization, Factory-CRO (Bilthoven, The Netherlands), was responsible for study conduction and monitoring, which included on-site monitoring visits. Clinically relevant endpoints, including vascular and bleeding complications, were adjudicated according to the latest VARC definitions (6).

Statistical analysis

Statistical analysis was conducted using SPSS version 21.0.01 (IBM Corp., Armonk, New York). Continuous variables are presented as mean ± SD or as median (interquartile range), and categorical variables are expressed as percentages. Repeated measurements in individual patients were compared using a paired Student t test.

RESULTS

A total of 50 patients were included from 3 European centers between July 2015 and January 2016. Overall, 9 different operators deployed the MANTA VCD. None of the operators had MANTA experience before entering the study. Baseline demographics are displayed in Table 1. Mean age was 79.5 ± 8.3 years. Women represented 54% of the cohort. The Society of Thoracic Surgeons predicted risk of mortality (STS PROM) was 5.8 ±4.3. Procedural characteristics are summarized in Table 2. One patient underwent high risk percutaneous coronary intervention with a 14-F circulatory support system, 2 patients underwent balloon aortic valvuloplasty, and 47 patients

	N=50
Age, yrs	79.5 ± 8.3
Female	27 (54)
Weight, kg	75.3 ± 15.6
STS score	5.85 ± 4.31
Prior CABG	1 (2)
Prior PCI	6 (12)
Pacemaker	2 (4)
Atrial fibrillation	1 (2)
Stroke	2 (4)
COPD	2 (4)
Hemodialysis	1 (2)
Creatinine, mmol/l	116 ± 79
Hemoglobin	12.20 ± 1.66

Table 1. Baseline patient characteristics. Values are mean SD or n (%). Abbreviations: CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons.

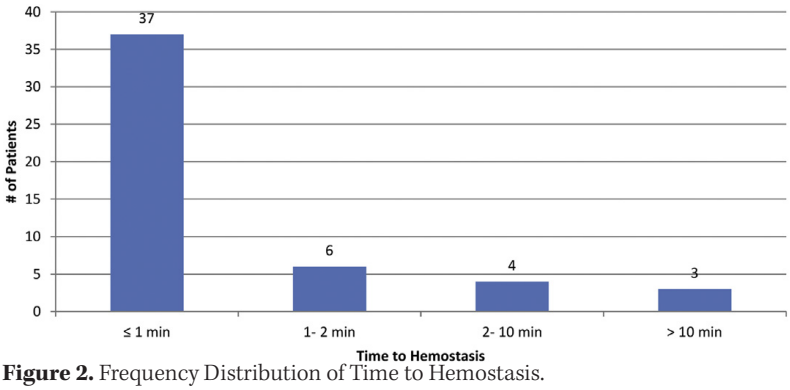

Figure 2. Frequency Distribution of Time to Hemostasis.

Procedure and Device	Procedure Sheath	Sheath OD Profile (French)	n	MANTA Size
Balloon aortic valvuloplasty	12-F to 14-F Cook*	16–18	2	14-F
Evolut R TAVR†	Sheathless 14-F	18	13	14-F
Continuous flow Circulatory support device‡	14-F	18	1	14-F
Evolut R TAVR†	Sheathless	18	4	18-F
Portico TAVR§	19-F SoloPath ‖	23	1	18-F
Direct Flow TAVR¶	18-F Direct Flow¶	22	5	18-F
CoreValve TAVR†	18-F CoreValve†	22	2	18-F
Lotus TAVR (23 mm)#	Small Lotus#	22	5	18-F
Sapien 3 TAVR (23 and 26 mm)**	14-F e-Sheath**	23	9	18-F
Lotus TAVR (25 and 27 mm)#	Large Lotus#	24	3	18-F
Sapien 3 TAVR (29 mm)**	16-F e-Sheath**	24.5	5	18-F

Table 2. MANTA Size Selection per Procedure Type and Sheath Size. *Cook Medical, Bloomington, Indiana. †Medtronic, Fridley, Minnesota. ‡Thoratec, Pleasanton, California. §St. Jude Medical, Little Canada, Minnesota. ‖ Terumo Interventional Systems, Somerset, New Jersey. ¶Direct Flow Medical, Santa Rosa, California. #Boston Scientific, Marlborough, Massachusetts. **Edwards Lifesciences, Irvine, California. OD = outer diameter; TAVR = transcatheter aortic valve replacement.

TAVR. The large-bore sheath size varied from an internal diameter of 12-F to 19-F, including the use of expandable 14-F and 16-F e-sheaths, with ODs ranging between 14-F and 24.5-F. The 14-F MANTA VCD was applied in one-third of the overall cohort (16 of 50, 32%), including all non-TAVR patients, and the 18-F MANTA VCD in the remainder.

The MANTA VCD was deployed successfully in all patients. Forty-seven of the 50 patients (94%) met the primary performance endpoint of hemostasis success. The mean TTH was 2 min, 23 s. The median TTH was 24 s, with 74% of the patients having hemostasis in <1 min (Figure 2). All-cause mortality at 30 days was 8% (n = 4), none of the deaths were related to the MANTA device or access site. One patient had a minor stroke. Overall, 12 patients required packed red blood cell (RBC) transfusions, but none were for MANTA access site–related issues (Table 3). A total of 6 patients needed 1 unit of packed RBC, 4 patients needed 2 RBC, and 2 patients needed 4 RBC. According to VARC-2 definitions, 1 patient experienced a major vascular and major bleeding complication with prolonged femoral bleeding that was successfully treated with a covered stent and eventual surgical repair because of persistent oozing while needing emergency valve

Hemostasis success, %	
Overall	94
14-F	100
18-F	91.2
Time to hemostasis, mm:ss	00:24 (00:02–37:10)
*Safety**	
All-cause death	4 (8)
Major stroke	0
Minor stroke	1 (2)
VARC bleeding	
Life-threatening/disabling	0
Major	1 (2)
VARC vascular complications	
Major	1 (2)
Minor	0
Hemoglobin	12.20 ± 1.66
Need for any RBC	12 (24)
RBC per patient if RBC required	1.5 (1–4)

Table 3. MANTA Effectiveness and Safety (N = 50). Values are n, median (interquartile range), n (%), or mean SD. *Defined according to the Valve Academic Research Consortium (VARC). Abbreviations: mm:ss = min:s; RBC = packed red blood cells.

surgery for a misplaced TAVR device. There were no VARC-2 minor vascular complications. One patient needed prolonged balloon inflation to control bleeding (minor bleeding according to VARC-2), and 1 patient needed balloon inflation to treat a pseudoaneurysm. Five patients presented with subcutaneous hematomas without further medical intervention.

Angiography showed widely patent femoral vessels in all subjects (Figure 3). In 3 patients, there was angiographic evidence of extravasation. As described in the preceding text, 2 of these were resolved with femoral balloon inflation, and 1 was repaired surgically as the patient proceeded to emergent surgical

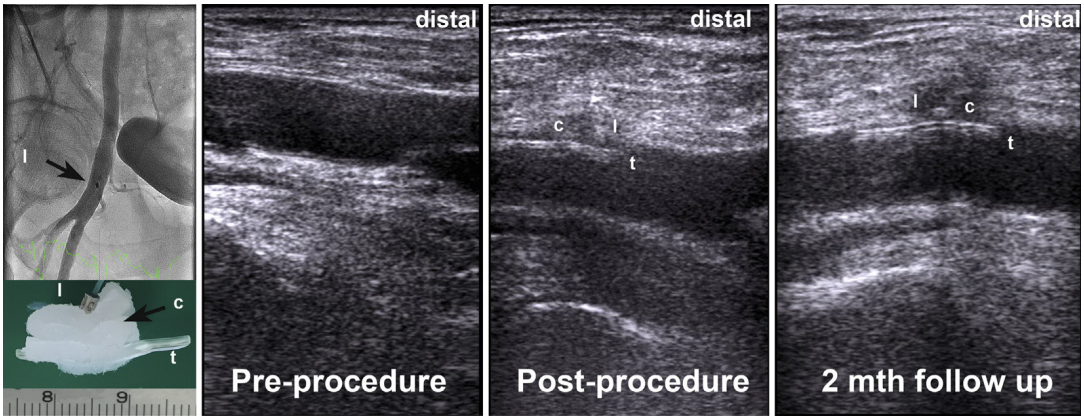

Figure 3. MANTA angiographic and ultrasound appearance. (Left upper panel) Angiogram shows the position of the "Manta-plug" in the femoral artery, visible by the metal cm marker appearing as a black spot (black arrow). (Bottom left panel) Macro photograph of the plug. The poly-lactate toggle, the collagen, and the nitinol lock are respectively indicated by t, c, and l. Longitudinal ultrasound images of the femoral artery were acquired before the procedure, post-procedure, and at 2 months follow-up. The poly-lactate toggle (t) is visible in the lumen against the vessel wall as a long double-layered bright structure. The collagen (c) appears as a darker area.

valve replacement. Duplex studies immediately post-deployment and at discharge confirmed patency in all vessels. Ultrasound evidence showed stability of the absorbable, intravascular MANTA anchor and extravascular collagen layer up to 60 days. Ankle brachial indices remained stable over the study period: 1.09 ± 0.19 at baseline, 1.01 ± 0.10 at discharge, and 1.02 ± 0.17 at later follow-up ($p = 0.111$). There were no late vascular complications related to the MANTA device.

DISCUSSION

The prospective multicenter MANTA CE mark study demonstrates rapid and reliable vascular hemostasis after 12-F to 19-F (OD 16-F to 24.5-F) transfemoral arteriotomies with this second-generation, dedicated, large-bore vascular closure device. MANTA VCD was applied in various completely percutaneous interventions including TAVR, balloon aortic valvuloplasty, and mechanical circulatory support.

Vascular and bleeding complications in the MANTA CE mark study were low despite the operators' inexperience with the novel closure device. Overall, vascular complications according to VARC-2 were encountered in 1 patient (2%), including 1 major and 0 minor complications. The CONTROL (Closure Device in Transfemoral Aortic Valve Implantation) multicenter study included 944 patients undergoing

TAVR and suture-based arteriotomy closure with either Prostar XL or Perclose Proglide (Abbott Vascular, Redwood City, California) in a propensity matched analysis. VARC major and minor vascular complications were noted in 7.4% and 14.8% with Prostar and 1.9% and 18% with Proglide, respectively (3). Importantly, operators participating in the CONTROL study were experienced with the respective suture-based closure devices, whereas the MANTA study represented the initial learning curve of the participating operators.

A study on 380 consecutive patients undergoing balloon aortic valvuloplasty with a sheath size ranging from 9-F to 13-F reported serious vascular complications, including arterial perforation, pseudoaneurysm formation, arteriovenous fistula, and leg ischemia in 5.5% to 6.7% depending on the closure device used (7). A single-center study including 274 patients undergoing transfemoral TAVR with either surgical cut-down and repair, or suture-based percutaneous closure showed similar acute closure success and access site–related events but more femoral stenosis and dissection with the percutaneous closure (7.1% vs. 0.7%; p = 0.007) and more wound infections and need for surgical debridement with the surgical approach (0.7% vs. 6.7%; p = 0.007) (8). The completely percutaneous approach reduced procedural time and patient morbidity. Comparison of clinical endpoints like vascular complications across different studies may be difficult because of nonuniformity in endpoint definitions and reporting bias in the absence of independent clinical event adjudication. The VARC is an initiative by research organizations, academics and regulatory instances to provide consensus definitions on important clinical endpoints (6). These VARC endpoints are currently well adopted and allow more reliable data comparison. In randomized TAVR versus surgical aortic valve replacement trials with controlled and independently adjudicated outcome data, vascular complications were consistently more frequent with TAVR (5.9% vs. 1.7%; p = 0.003, in the U.S. CoreValve High-Risk study and 11.3% vs. 3.8%; p < 0.001, in the PARTNER (Placement of Aortic Transcatheter Valve) Cohort A), whereas disabling, life-threatening, or major bleedings occurred more often with surgical aortic valve replacement (35% vs. 13.6%; p < 0.001, in the U.S. CoreValve High-Risk study, and 26.7% vs. 15.7% in PARTNER Cohort A) (9,10). Over time, the rate of vascular complications has gradually declined due to growing experience, improved access technique with fluoroscopic or ultrasound guidance, and design modifications with smaller profile devices (11,12). Also, additional maneuvers such as the cross-over balloon technique may create a low pressure milieu for optimal closure device functioning at the time of sheath removal and facilitate the percutaneous management of vascular complications (13,14). A relatively small single-center study on 137 patients reported a low rate of major and minor vascular complications of 1% and 8%, respectively (12). However, contemporary rigorous trials with independent clinical event adjudication still report major vascular complications after TAVR in >5% of patients, and two-thirds of these major complications are due to failed arteriotomy closure (1,2,4). Therefore, in the current era, and despite growing operators' experience, vascular complications are still a limitation of TAVR and other large bore interventions. These vascular complications, bleedings, and the need for transfusions are associated with worse clinical outcomes and thus warrant further improvements in access site management (15).

Plug-based closure is well established for 5-F to 8-F arteriotomies and among the most widely used globally (16). It reduces TTH, promotes early patient ambulation, and improves patient satisfaction compared with manual compression (17,18). So far, no head-to-head comparisons between plug-based and suture-based closure devices exist. One meta-analysis on percutaneous vascular closure devices suggested that only plug-based closure reduced major vascular complications compared with manual compression

(odds ratio: 0.51; 95% confidence interval 0.45 to 0.58), with a neutral effect for suture-based closure (odds ratio: 1.0, 95% confidence interval: 0.13 to 7.48) (19). Clearly, no convincing data have proven the superiority of one closure technique over the other. Of note, for MANTA closure, a prophylactic cross-over balloon technique does not seem beneficial because it is felt that a pressurized vessel is best for spreading the collagen pad over the arteriotomy defect, and collagen in contact with blood and tissue factor is required to develop a stabilizing layer. MANTA closure failure can theoretically occur when the endovascular toggle does not connect with the arteriotomy from the inside (e.g., because it was caught by plaque), the plug does not connect with the vessel wall at the arteriotomy from the outside (e.g., because a growing subcutaneous hematoma has extended the subcutaneous track, and the depth has been underestimated), or too much pulling force has been applied, and the toggle is pulled outside of the vessel. Bail-out strategies in case of MANTA closure failure include prolonged endovascular balloon inflation and manual compression, covered stent placement, or vascular surgery.

Study limitations

A limitation of the MANTA CE mark study is its relatively small sample size and its nonrandomized nature. Selection bias may have affected the reported clinical results. Yet the involvement of an independent clinical research organization with rigorous data monitoring and the favorable results should spur further research in larger studies, preferably including randomized trials comparing MANTA VCD with current suture-based closure techniques.

CONCLUSIONS

The MANTA VCD is a novel, collagen plug-based, large-bore closure device. It targets large-bore procedures requiring devices up to 19-F (true OD profiles up to 24.5-F). This initial multicenter experience demonstrated rapid and reliable hemostasis and low complication rates. Broader community-based experience and randomized trials comparing the MANTA device to alternative techniques are warranted.

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Part III
Neurological events

CHAPTER IX

Embolic protection devices in transcatheter aortic valve implantation

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EuroIntervention 2015;11:247-8

BACKGROUND AND INDICATIONS

As the technique of transcatheter aortic valve implantation (TAVI) is maturing and its application broadening, reduction of TAVI related complications is crucial. TAVI has proven to be superior to medical therapy in inoperable patients with aortic stenosis (AS) and at least as effective as surgical aortic valve replacement (SAVR) in AS patients at high risk for perioperative complications and mortality (1,2). The first randomized trials seemed to suggest that clinically overt neurological events complicated TAVI in comparison to medical therapy or the more invasive SAVR (1,2). Recently the randomized CoreValve US Pivotal trial refuted this premature notion. In a carefully designed trial setting encompassing neurologists who assessed patients before and after aortic valve replacement, there was no difference in clinical neurological events between TAVI and SAVR (3). Nevertheless, TAVI implies: 1) the use of large-bore catheters, 2) passage through an aged and diseased aortic arch and ascending aorta, 3) crossing of a calcified and degenerated aortic valve, 4) positioning and deployment of a transcatheter valve within the diseased native aortic valve, and 5) passage and maneuvering of guidewires within the left ventricle. Brain magnetic resonance imaging (MRI), transcranial Doppler and histopathology studies have revealed that cerebral embolization is inherent to TAVI (4-8). Although most TAVI cases seem uneventful from a clinical neurological perspective, silent brain ischaemia and defects occur in up to 80% of patients (9). These silent brain lesions and micro infarcts may not be so harmless after all, as an association with premature neurocognitive impairment seems established (10-12). This global brain dysfunction (i.e., slight cognitive decline, memory and mood disturbances, reduction of psychomotor speed, and personality changes) might be easily missed during routine neurological examination (13). Especially in patients with a longer life expectancy, these events may thus become clinically and socially relevant. Cerebral embolic protection devices (EPDs) may reduce intraprocedural cerebral embolization which may be associated with silent brain ischaemia and subsequent infarct.

TOOLS AND TECHNIQUES

Currently, three different EPDs with two fundamentally different designs have obtained a CE mark for use in TAVI.

Triguard

The TriGuard embolic deflection device (Keystone Heart Ltd., Caesarea, Israel (previously known as SMT Research & Development)) is a single-use, biocompatible mesh made of fine nitinol wires with pores of 130 µm and an antithrombotic coating (Applause™ Heparin Coating; SurModics, Inc., Eden Prairie, MN, USA) (Figure 1) (14,15). The TriGuard mesh forms a barrier and subsequently deflects emboli downstream. It contains two stabilisers for optimal positioning and stability. It covers the ostia of the brachiocephalic trunk, the left common carotid artery and the left subclavian artery. An atraumatic stabiliser in the brachiocephalic trunk supports the position throughout the procedure.

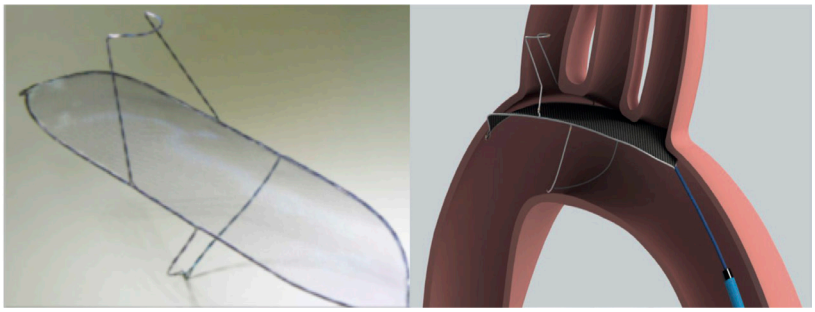

Figure 1. The TriGuard embolic deflection device. The TriGuard embolic deflection device has a nitinol frame which contains a nitinol mesh with 250 (and in the latest design 130) um pores and antithrombotic coating. It contains two stabilisers for optimal positioning and stability. It covers the ostia of the brachiocephalic trunk, the left common carotid artery and the left subclavian artery. An atraumatic stabiliser in the brachiocephalic trunk supports the position throughout the procedure.

Technique

The device is delivered through a transfemoral access using a 9 Fr Mullins introducer sheath (Medtronic, Minneapolis, MN, USA). The sheath is advanced beyond the aortic arch take-offs. While holding the TriGuard in place, the sheath is pulled back to expand the device in the aortic arch. The atraumatic stabiliser extends into the brachiocephalic trunk to anchor the TriGuard. Optimally, the mesh protects all major arterial contributories to the brain by deflecting debris and maintaining blood flow. Device positioning on average takes 11 minutes (15). Of note, in the "Prospective, Randomized Evaluation of the TriGuard™ HDH Embolic Deflection Device During Transcatheter Aortic Valve Implantation" (DEFLECT-III) trial, mean total fluoroscopy time was 10 minutes longer (28.4 vs. 18.8 min, $p<0.001$) in TriGuard subjects compared with controls (16). After transcatheter heart valve implantation, the TriGuard is pulled back into the Mullins sheath and retrieved from the body.

Device limitations

The TriGuard is currently the only commercially available EPD that potentially covers all extracranial

cerebral vessels. The overall profile mandates 9 Fr femoral access, which may increase the risk of vascular complications. Device stability may vary during THV navigation through the aorta. The "Prospective, Single Arm Feasibility Study to Evaluate the Safety and Performance of the SMT Embolic Deflection Device in Patients Undergoing Transcatheter Aortic Valve Replacement" (DEFLECT-I) and the DEFLECT-III trials revealed device instability in 36% and 11%, respectively (15,16). Furthermore, in the DEFLECT-II trial, the TriGuard interfered with balloon and THV systems in 36% of cases (17). Excessive atherosclerotic disease in the aortic arch, particularly at the outer curve, may pose a relative contraindication for use.

Embrella embolic deflector

The Embrella Embolic Deflector system (Edwards Lifesciences, Irvine, CA, USA) consists of a porous polyurethane membrane within a nitinol frame (Figure 2) (18). The pore size is 100 μm and the membrane contains a hydrophilic coating with antithrombotic properties. The Embrella forms a barrier and subsequently deflects emboli downstream (18-20). Of note, in the majority of cases the ostium of the left subclavian artery will not be covered; therefore, the posterior part of the brain which is vascularised by the left vertebral artery may not be protected from potential emboli (Figure 2).

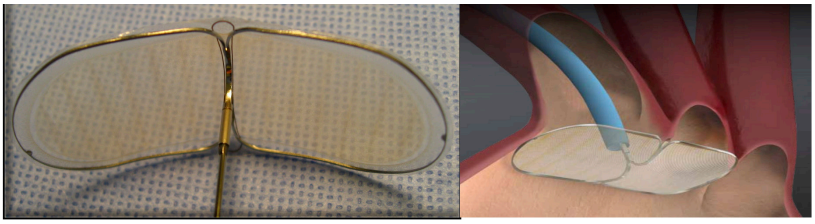

Figure 2. The Embrella Embolic Deflector system. The Embrella Embolic Deflector system has an oval-shaped nitinol frame with a polyurethane membrane with 100 um pores. The frame has two opposing petals which cover the ostia of the brachiocephalic trunk and the left common carotid artery.

Technique

Access is gained via a right radial (or brachial) artery approach. A 0.035" or 0.038" guidewire is advanced under fluoroscopic guidance and positioned in the brachiocephalic artery ostium. A 6 Fr (90 cm) Flexor® Tuohy-Borst Sidearm Introducer sheath (Shuttle®-SL; Cook Medical, Bloomington, IN, USA) is advanced over the wire into the aorta. The Embrella is inserted into the sheath with an Embrella loading tool and advanced up to the ostium of the brachiocephalic trunk. The assembly is then pushed outside of the sheath and the device petals fold open in the aortic arch. The system is then fully deployed and should be pulled back to be apposed to the greater curvature of the aortic arch to cover the ostia of the brachiocephalic trunk and the left common carotid artery. Three radiopaque markers on the petals facilitate device positioning. A contrast injection through the introducer sheath side port or a pigtail catheter can confirm proper device positioning within the aorta. The device is then locked in place by tightening the Tuohy-Borst adapter on the introducer sheath and fixating the "Embrellasystem Shaft Torquer" proximal to the Tuohy-Borst adapter. An adhesive dressing is placed on the skin at the insertion site. A pressure sensor is attached to the side port of the introducer sheath to monitor systemic arterial pressure while the Embrella is in place. The Embrella in situ requires full anticoagulation with ACT levels >300 seconds. In the PROTAVI-C study, the median time for Embrella deployment was 2 min (IQR 1 to 3 min). After

transcatheter heart valve implantation, the Embrella is retrieved by pulling the device into the introducer sheath. During this maneuver it is paramount to immobilise the sheath at the level of the ostium of the brachiocephalic trunk.

Device limitations

The Embrella covers three of four entry routes to the Willis polygon, leaving the left vertebral artery unprotected (21). The Embrella does not seem to interfere with the transcatheter valve system during TAVI, yet the introduction and deployment of the device itself seem to result in more high-intensity transient signals (HITS) by transcranial Doppler and ischaemic cerebral lesions by MRI (19,20). Excessive atherosclerotic disease in the aortic arch – particularly at the outer curve – and brachiocephalic trunk may pose a relative contraindication for use.

Sentinel

The Sentinel™ dual filter system (Claret Medical Inc., Santa Rosa, CA, USA) is delivered through a 6 Fr sheath, which is inserted transradially or transbrachially (Figure 3) (22). The Sentinel is a 100 cm co-axial, steerable sheath housing two cone-shaped filters made of 140 µm pore size biocompatible polyurethane film. The proximal filter is deployed into the brachiocephalic trunk and accommodates vessel sizing of 9 to 15 mm in diameter. The dedicated handle is designed to articulate the distal segment of the catheter to navigate through the aortic arch and direct the tip of the system into the left common carotid artery to deploy the distal filter, which is smaller and fits within 6.5 to 10 mm vessels.

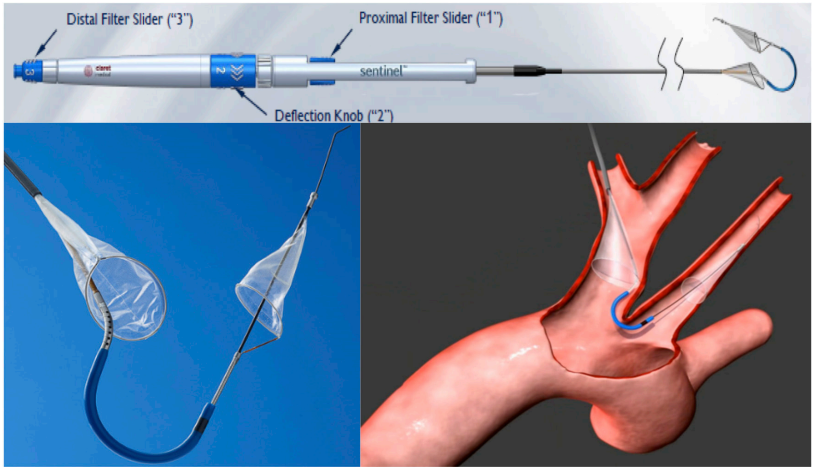

Figure 3. The Sentinel dual filter device. The Sentinel dual filter device consists of a steerable and rotatable catheter that contains two polyurethane mesh filters with 140 µm pores mounted on a nitinol frame. One filter is deployed in the brachiocephalic trunk and the other in the left common carotid artery.

Technique

The anatomical landing zones - the brachiocephalic trunk and the left common carotid artery – need to be assessed by contrast aortography or MSCT planning (Figure 4) to determine proper vessel size

for adequate apposition and protection. The central lumen of the delivery system is loaded with a 0.014" coronary guidewire which precedes the tip of the delivery system to facilitate navigation through the arterial tree of the upper extremity. The tip of the assembly is advanced into the ascending aorta so that the sheathed radiopaque frame of the proximal filter is positioned proximally within 30 mm of the ostium of the brachiocephalic trunk. With the sliding mechanism on the handle the proximal filter is deployed in the designated landing zone. The rotating knob on the handle can curve the distal portion of the catheter. The distal tip is pulled and oriented towards the left common carotid artery. The 0.014" wire is advanced into the left common carotid artery followed by the distal filter. Proper positioning can be confirmed using contrast injection. At the end of the TAVI procedure, the previous steps are reversed. The distal filter is pulled into the distal segment of the delivery system first, the curve is straightened and the proximal filter is re-sheathed.

Figure 4. Preprocedural MSCT planning with 3mensio software showing the most common aortic arch anatomy.

Device limitations

The Sentinel leaves the left vertebral artery unprotected. Excessive tortuosity in the arterial trajectory towards the filter landing zones precluded deployment in 4 to 9% of reported cases, and device interference with the pigtail catheter occurred in one case (2%) (22,23). The CLEAN-TAVI investigators reported a 90% procedure success with inability to deploy any of the filters due to excessive tortuosity of the arteries in 2/50 patients. Excessive tortuosity, significant atherosclerotic disease and small vessel size need to be ruled out prior to device insertion. Device interference with transfemorally inserted catheters and the THV delivery system is rare.

PERFORMANCE DATA

Clinical outcome

The thirty-day disabling stroke rate in elderly patients undergoing TAVI is <5% (24). Approximately half of these major neurological events occur within the first 24 hours and seem directly amenable to EPDs (25). Against this backdrop of relatively low incidence, surrogate endpoints are probably required to document the meaningful effects of the use of EPDs. Neurological outcomes for all EPDs are displayed in Table 1.

Study	DEFLECT-I (n=37) (15)	DEFLECT-II (n=14) (17)	DEFLECT-III (n=46) (16)	PROTAVI-C (n=41) (19)	Samim et al (n=15) (20)	Naber et al (n=40) (22)
Major stroke	2 (5.4%)	0 (0%)	2 (4.3%)	2 (4.9%)	0 (0%)	2 (5.0%)
Worsening NIHSS score	NA	NA	2 (4.3%)	0 (0.0%)	NA	3 (7.5%)

Table 1. 30-day neurological outcome for all embolic protection devices.

So far, none of the available EPDs has shown significant reductions in disabling clinical strokes. In DEFLECT-III, paired NIHSS assessments revealed "new neurologic impairment" in 3.1% of TriGuard-protected patients vs. 15.4% of controls (p=0.16). Neurocognitive testing has been proposed to document subtle changes in cognitive performance. A different battery of tests has been suggested but currently there is no consensus on which tests would be most suitable to evaluate EPD with TAVI. The Montreal cognitive assessment (MoCA) is frequently applied. In the PROTAVI-C pilot study, the Embrella EPD did not affect MoCA test results. In both DEFLECT-III and CLEAN-TAVI, fewer protected patients appeared to have worsening MoCA scores compared to controls (16,23).

DW-MRI

Diffusion-weighted magnetic resonance imaging (DW-MRI) has a high sensitivity for new ischaemic brain lesions. All available EPDs have been evaluated by brain MRI studies. Several MRI-specific caveats need to be considered before comparing these results. The MRI field strength is essential as it renders the study even more sensitive (26). A 3-Tesla scanner may yield a higher lesion detection rate than a 1.5-Tesla scanner. The acquisition of baseline MRI may be important to eliminate any visible pre-existing lesions and co-register the baseline against the follow-up MRI visible lesions. Size and number of lesions will change considerably throughout the first week after the procedure. Also, the impact of new clinical situations such as new-onset atrial fibrillation may induce new areas of brain ischaemia due to thromboembolisation. In the DEFLECT-III trial, use of the TriGuard EPD resulted in more patients with no lesions on brain MRI (Figure 5) (16). Also, total new lesion volume was reduced, although the number of lesions was similar (Figure 6, Figure 7). Use of the Sentinel showed significant reductions in the total number of lesions (50% reduction with p=0.002) at two days and reduced the overall total lesion volume compared to patients without EPD by more than 50% at two days (p=0.002) (23). Conversely, the PROTAVI-C pilot study demonstrated numerically more new lesions and overall larger total lesion volume with use of the Embrella EPD.

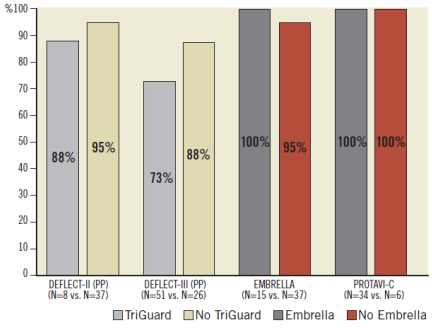

Figure 5. Proportion of patients in present studies with detected lesions on DW-MRI for different embolic protection devices compared with controls. Abbreviations: PP: per protocol group (16,17,19,20).

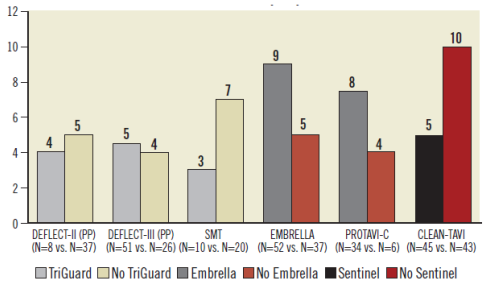

Figure 6. Number of lesions per patient detected on DW-MRI in the present studies for different embolic protection devices compared with controls (14,16,17,19,20,23).

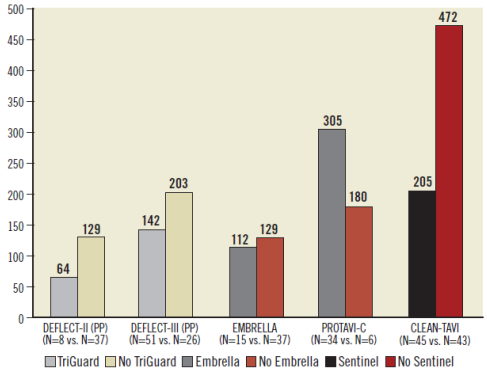

Figure 7. Total lesion volume per patient detected on DW-MRI in the present studies for different embolic protection devices compared with controls (16,17,19,20,23).

Current MRI data do not allow fair comparison between EPDs and selected THVs. For this purpose, head-to-head comparisons in the context of a randomised trial using identical MRI techniques and timing of follow-up MRI studies seem essential. However, MRI studies: 1) have major logistic limitations, 2) are not patient-friendly for elderly subjects due to concomitant noise and the relatively tight-fitting tube, 3) have not consistently had baseline MRI performed. Fourthly, new permanent pacemaker implantation post TAVI may pose a relative contraindication for MRI examination. Not surprisingly, follow-up MRI was not completed in 22% to 41% of patients in contemporary studies (16,19,23).

Transcranial Doppler

Transcranial Doppler (TCD) sonography can detect HITS that represent embolic activity, either solid or gaseous. HITS appear most commonly during THV implantation and deployment (5,27,28). Interpretation of TCD remains somewhat challenging, and overall TCD results with TAVI are controversial. In the PROTAVI-C study, deployment of the Embrella EPD generated approximately the same number of HITS as the THV deployment and a greater total number of HITS throughout the entire procedure (19). In DEFLECT-I, use of the TriGuard EPD generated fewer HITS than THV positioning and deployment. Interestingly, gaseous emboli were approximately three times more common than solid emboli during all stages of the procedure.

Histopathology

The filter-based Sentinel is the only EPD that allows capture and retrieval of debris en route to the brain. Embolic material was captured in 75 to 86% of patients in whom the filter was used (7,29). Debris could be either thrombotic or tissue-derived. Solid dislodged tissue debris was found in 52 to 63% of patients. Histopathological analysis revealed material from the native aortic valve leaflets, aortic wall and left ventricular myocardium.

FUTURE PERSPECTIVES

Device iterations

Each device described above may intuitively have room for improvement. Stability of embolic deflectors in the outer curve of the aortic arch may increase over time. Also, the likelihood of complete protection including left subclavian ostium coverage may be targeted. Similarly, filter protection of the left vertebral artery in addition to current Sentinel protection may be evaluated. Smaller device profiles may further reduce the risk for access-site complications, especially when using the femoral route.

Consensus

The Valve Academic Research Consortium (VARC) proposed uniform endpoint definitions which were widely adopted in clinical practice, registries and randomised trials. Similar consensus statements on trial designs, study endpoints and definitions may help interpret results of future EPD studies and allow relevant comparison. The participation of trained and certified neurology specialists (neurologists, nurse practitioners, etc.) is essential to detect reliably the sometimes subtle neurologic changes post TAVI. Neurocognitive assessment should rely on a standardised battery of neurocognitive tests. Optimal timing of post-procedural brain MRI studies as well as standardised MRI settings are mandatory to compare study results. Importantly, the value of brain MRI-based surrogate endpoints (number of lesions, lesion

volume, total lesion volume) needs validation and acceptance because the incidence of clinically apparent disabling strokes is low and the appearance of new subclinical brain lesions and micro-infarcts may truly pose meaningful threats to neurocognitive function and psychosocial wellbeing in lower-risk and younger patients with symptomatic severe AS who will arguably become the next target population for TAVI in the near future.

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CHAPTER X

Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial

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ABSTRACT

Aims

Our aim was to determine whether use of the filter-based Sentinel™ Cerebral Protection System (CPS) during transcatheter aortic valve implantation (TAVI) can affect the early incidence of new brain lesions, as assessed by diffusion-weighted magnetic resonance imaging (DW-MRI), and neurocognitive performance.

Methods and results

From January 2013 to July 2015, 65 patients were randomised 1:1 to transfemoral TAVI with or without the Sentinel CPS. Patients underwent DW-MRI and extensive neurological examination, including neurocognitive testing one day before and five to seven days after TAVI. Follow-up DW-MRI and neurocognitive testing was completed in 57% and 80%, respectively. New brain lesions were found in 78% of patients with follow-up MRI. Patients with the Sentinel CPS had numerically fewer new lesions and a smaller total lesion volume (95 mm3 (IQR 10-257) vs. 197 mm3 (95-525)). Overall, 27% of Sentinel CPS patients and 13% of control patients had no new lesions. Ten or more new brain lesions were found only in the control cohort (in 20% vs. 0% in the Sentinel CPS cohort, p=0.03). Neurocognitive deterioration was present in 4% of patients with Sentinel CPS vs. 27% of patients without (p=0.017). The filters captured debris in all patients with Sentinel CPS protection.

Conclusions

Filter-based embolic protection captures debris en route to the brain in all patients undergoing TAVI. This study suggests that its use can lead to fewer and overall smaller new brain lesions, as assessed by MRI, and preservation of neurocognitive performance early after TAVI.

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is less invasive and results in faster recovery and improvement in quality of life as compared to surgical aortic valve replacement (SAVR) (1-6). In selected patients TAVI also reduces one-year mortality (7). Major stroke is still a vexing complication associated with aortic valve replacement (8). Recent studies suggest similar stroke rates with SAVR and TAVI, varying between 2 and 10% (9). Transcranial Doppler (TCD) and brain diffusion-weighted magnetic resonance imaging (DW-MRI) studies revealed, respectively, cerebral high-intensity transient signals (HITS) and new ischaemic brain lesions in up to 90% of all patients undergoing TAVI (10-13). Approximately half of all strokes within 30 days after TAVI occur in the first 24 hours and are thus directly related to the procedure (14-16). TAVI inevitably releases debris from the aortic wall, the aortic annulus and even from cardiac structures, and catheter-related foreign body particles (17,18). Recently, the randomised DEFLECT III trial demonstrated fewer DW-MRI-detected ischaemic brain lesions and less cognitive decline with the use of the TriGuard cerebral embolic protection device (Keystone Heart Ltd., Caesarea, Israel) (19). The Sentinel™ Cerebral Protection System (CPS) (Claret Medical Inc., Santa Rosa, CA, USA) provides filter protection to the brachiocephalic trunk and the left common carotid artery. The safety and efficacy of the device were demonstrated and the device obtained CE mark in January 2014 (20). Furthermore, recent pathology studies have confirmed capture of debris with the Sentinel CPS in 75 to 86% of all patients undergoing TAVI (17,21). The clinical impact of this embolised debris into the brain and consequent new ischaemic brain lesions by DW-MRI is controversial, but silent brain infarcts have been correlated with premature neurocognitive deterioration and dementia (22,23). The aim of the randomised MRI Investigation in TAVI with Claret (MISTRAL-C) study (Dutch trial register-ID: NTR4236) is to determine whether use of the Sentinel CPS during TAVI can decrease the incidence of new brain lesions as assessed by DW-MRI, and can prevent neurocognitive decline.

METHODS

The MISTRAL-C was a multicentre double-blind randomised trial. All eligible patients underwent multimodality imaging, including multislice computed tomography (MSCT) scan of the aortic valve and the arterial vasculature. Patients were deemed at high risk for SAVR and selected for transfemoral TAVI by Heart Team consensus. Aortic arch anatomy had to fit the sizing requirements for the Sentinel CPS: the brachiocephalic trunk and left common carotid artery should range between 9 and 15 mm and 6.5 and 10 mm, respectively, without excessive tortuosity or >70% obstructive atherosclerotic disease. Key exclusion criteria were the presence of a permanent pacemaker or automated internal cardiac defibrillator (AICD) at baseline, a history of prior stroke with sequelae and dementia. Patients were randomised 1:1 to TAVI with or without the Sentinel CPS. Per protocol, a DW-MRI scan and extensive neurological examination were performed one day before and planned again five to seven days after TAVI. One dedicated experienced neuroradiologist independently read all MRI studies. A trained neurology specialist performed a comprehensive neurological exam, including the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS), and a neurocognitive evaluation with the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE) (24,25). The Center for Epidemiologic Studies Depression scale (CES-D) was used to rule out significant depression. The neuroradiologist and

neurology specialists were blinded to the randomisation arm. The most recent Valve Academic Research Consortium definitions were applied to report relevant clinical endpoints (26). The local institutional review board at each site approved the study protocol, all subjects provided written informed consent, and the study was conducted in accordance with the principles of the Declaration of Helsinki. The Erasmus Medical Center received a research grant from Claret Medical which partially covered study-related expenses. The authors are fully responsible for the study design, study execution and drafting of the manuscript.

Sentinel CPS

The Sentinel CPS is a 6 Fr-compatible 100 cm coaxial, steerable sheath housing two cone-shaped filters made of a 140 μm pore size biocompatible polyurethane film. The device is inserted using a right radial or brachial arterial access. The proximal filter is first deployed into the brachiocephalic trunk. The distal segment of the catheter can then articulate to navigate through the aortic arch and into the left common carotid artery where the distal filter is deployed (Figure 1). At the end of the TAVI procedure, the previous steps are reversed.

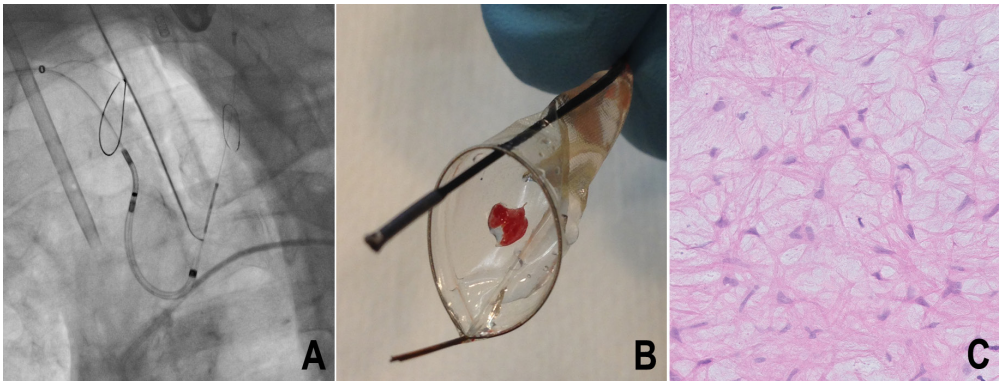

Figure 1. Sentinel dual filter system. A) Fluoroscopic image of the Sentinel CPS after deployment in the brachiocephalic trunk and left common carotid artery. B) Photograph of a retrieved filter containing embolic debris. C) Microscopic image showing the lamina spongiosa of the aortic valve (H&E staining, magnified ×20).

Magnetic resonance imaging

The MRI exam was performed with a 3.0 Tesla scanner with an 8-channel head coil. The MRI protocol consisted of three sequences: 1) transverse DW-MRI sequence with a b-value of 0,500,1000 s/mm^2 (SE/EPI, TR 8,000 ms, TE 80 ms, FOV 24×24 cm, matrix 128×128, slice thickness 3.6 mm, 3 NEX); 2) sagital 3D-FLAIR sequence (TR 6,500, TE 115, FOV 26×26 cm, matrix 224×224, slice thickness 1.2 mm, NEX 1); 3) 2D-T2w TSE sequence (TR 5,000 ms, TE 105 ms, FOV 24×24 cm, matrix 416×384, slice thickness 3 mm, NEX 2). The number, location, and volume (cm) of new hyperintense lesions were recorded. New lesions were allocated to the cerebellum, or the left or right vascular territory of the anterior, medial or posterior cerebral artery. To calculate the volume of hyperintense lesions on DWI, a semi-automated segmentation method was developed using MeVisLab (MeVis Medical Solutions AG, Bremen, Germany) (27). The brain was arbitrarily divided into Sentinel CPS protected and unprotected regions. Unprotected regions are

vulnerable to embolisations coming from the unprotected left vertebral artery, which corresponds to the cerebellum and the vascular territory of both posterior cerebral arteries.

Histopathology

Filters were retrieved and released from the delivery system, stored in a buffered formalin (4%) solution. Debris was dehydrated, embedded in paraffin and cut into 3 to 4 mm thick sections. Staining was done with haematoxylin and eosin and Movat pentachrome. Additional staining techniques were performed whenever applicable to identify specific tissue origin, as previously described (17).

Statistical analysis

Power analysis was based on the primary endpoint of new cerebral lesions by DW-MRI five to seven days after TAVI. To reach a reduction from 80% to 40% in volume of new ischaemic lesions by DW-MRI (standard deviation 50%) with the Sentinel CPS and based on the continuity-corrected chi-square test, we estimated that 54 patients (27 in each treatment arm) would be needed with an 80% power and a two-sided alpha of 0.05. To balance a potential 20% drop-out in MRI follow-up, 65 patients would be needed to obtain 54 patients with MRI before and after TAVI. Continuous variables were displayed as either mean±standard deviation or median with interquartile range, depending on distribution. Normality was tested by use of histograms and the Shapiro-Wilk test. Normally distributed variables were compared using a Student's t-test, while non-normally distributed variables were compared using the Kruskal-Wallis test. Categorical variables were displayed as frequencies and percentages. A chi-square test for equality of proportions was used for trends. Between-group comparisons for new brain lesions and neurocognitive function were restricted to patients with MRI or neurocognitive testing pre and post TAVI. Binary outcomes were compared using log-linear regression and were displayed as relative risks. All statistical analyses were performed with SPSS, Version 22 (IBM Corp., Armonk, NY, USA).

RESULTS

From January 2013 to July 2015, 65 patients were randomised 1:1 to transfemoral TAVI with or without cerebral protection with the Sentinel CPS (Figure 2) at four centres. Table 1 depicts baseline characteristics. The median age was 81 years (IQR 78-85) and 52% were male. The STS predicted risk of mortality was 4.8% (IQR 3.4-7.2), and appeared higher in the control cohort (STS 6.6 (IQR 3.8-9.9) vs. 4.6 (IQR 3.4-6.4)). Frailty was common (68%). A prior history of neurological events was present in 19% of patients. The distribution of the different transcatheter valve designs is displayed in Figure 3. The Sentinel CPS was successfully deployed in all but two patients. In one patient no Sentinel CPS was inserted because

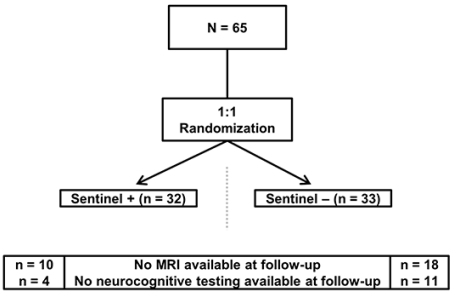

Figure 2. Patient flow diagram including follow-up missing for MRI and neurocognitive testing.

Baseline characteristics	Sentinel (n=32)	No Sentinel (n=33)	Total (N=65)	P-value
Age, median (IQR)	82 (79-84)	82 (77-86)	82 (78-85)	0.505
Female, n (%)	15 (47%)	16 (49%)	31 (48%)	0.897
Hypertension, n (%)	21 (66%)	23 (70%)	44 (68%)	0.726
Diabetes, n (%)	4 (13%)	9 (27%)	13 (20%)	0.137
Dyslipidaemia, n (%)	12 (38%)	17 (52%)	29 (45%)	0.256
Angina pectoris, n (%)	6 (19%)	9 (27%)	15 (23%)	0.415
Previous myocardial infarction, n (%)	2 (6%)	2 (6%)	4 (6%)	0.975
Atrial fibrillation, n (%)	8 (29%)	8 (27%)	16 (28%)	0.871
Peripheral arterial disease, n (%)	9 (28%)	11 (33%)	20 (31%)	0.649
Previous TIA/CVA, n (%)	6 (19%)	6 (18%)	12 (19%)	0.953
New York Heart Association Class, n (%)				
II	5 (20%)	6 (21%)	11 (20%)	
III	18 (72%)	19 (66%)	37 (69%)	0.782
IV	2 (8%)	4 (14%)	6 (11%)	
Left ventricular ejection fraction, % (mean±SD)	57±14	53±16	55±15	0.408
STS score, median (IQR)	4.6 (3.4-6.3)	5.8 (3.5-9.8)	4.8 (3.4-7.2)	0.029
Frail, n (%)	20 (65%)	23 (72%)	43 (68%)	0.530
Porcelain aorta, n (%)	4 (13%)	4 (13%)	8 (13%)	0.962

Table 1. Baseline characteristics. Abbreviations: CVA = cerebrovascular accident; STS PROM = Society of Thoracic Surgeons predicted risk of mortality; TIA = transient ischaemic attack.

of protracted haemodynamic instability after induction of general anesthesia. One patient was a screening failure and presented with an anatomic anomaly (arteria lusoria) that precluded Sentinel CPS placement. There were no device-related injuries.

Clinical endpoints at 30-day follow-up are summarised in Table 2. Overall, all-cause mortality at 30 days was 3%. Two patients – both in the unprotected cohort – suffered a disabling stroke and died within 30 days. Twelve patients (19%) needed a new permanent pacemaker after TAVI.

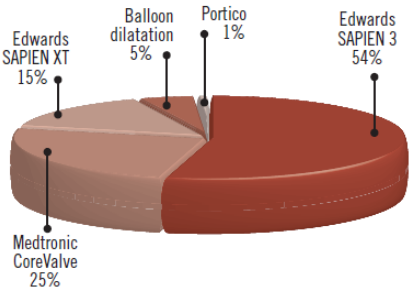

Figure 3. Relative proportion of various transcatheter heart valve designs used in the trial.

	Sentinel (n=32)	No Sentinel (n=33)	Total (N=65)	Relative risk [95% CI]	P-value
Dead after 5 days	1 (3%)	0 (0%)	1 (2%)	NA	NA
Dead after 30 days	1 (3%)	3 (10%)	4 (7%)	0.36 [0.04-3.43]	0.371
Dead after 6 months	1 (5%)	4 (17%)	5 (11%)	0.27 [0.30-2.44]	0.245
Stroke					
Non-disabling	0 (0%)	0 (0%)	0 (0%)	NA	NA
Disabling	0 (0%)	2 (7%)	2 (3%)	NA	NA

Delirium	1 (3%)	5 (15%)	6 (9%)	0.21 [0.02-1.77]	0.150
New permanent pacemaker	7 (23%)	5 (16%)	12 (19%)	1.45 [0.46-4.55]	0.529
Coronary obstruction	0 (0%)	1 (3%)	1 (2%)	NA	NA
Valve embolisation	0 (0%)	0 (0%)	0 (0%)	NA	NA
Cardiac tamponade	0 (0%)	2 (6%)	2 (3%)	NA	NA
Myocardial infarction	0 (0%)	2 (6%)	2 (3%)	NA	NA
Acute kidney injury	0 (0%)	1 (3%)	1 (2%)	NA	NA
Bleeding within one day					
Any bleeding	10 (32%)	14 (44%)	24 (38%)	0.74 [0.33-1.66]	0.462
Minor	9 (29%)	9 (28%)	18 (29%)	1.03 [0.41-2.60]	0.946
Major	1 (3%)	0 (0%)	1 (2%)	NA	NA
Life-threatening	0 (0%)	5 (16%)	5 (8%)	NA	NA
Bleeding after one day					
Any bleeding	9 (29%)	13 (41%)	22 (35%)	0.72 [0.31-1.67]	0.438
Minor	8 (26%)	12 (38%)	20 (32%)	0.69 [0.28-1.68]	0.413
Major	0 (0%)	1 (3%)	1 (2%)	NA	NA
Life-threatening	1 (3%)	0 (0%)	1 (2%)	NA	NA
Vascular complications					
Any vascular complication	12 (39%)	19 (59%)	31 (49%)	0.65 [0.32-1.34]	0.246
Minor	12 (39%)	13 (41%)	25 (40%)	0.95 [0.44-2.09]	0.904
Major	0 (0%)	6 (19%)	6 (10%)	NA	NA

Table 2. Clinical endpoints at 30-day follow-up. Valve Academic Research Consortium-2 (VARC) definitions were applied.

Brain MRI

Baseline brain MRI assessment confirmed ischaemic lesions in 11% of patients. Follow-up MRI was completed in 57% of the patients a mean of 5.0±1.1 days post TAVI. Twenty-eight patients did not undergo

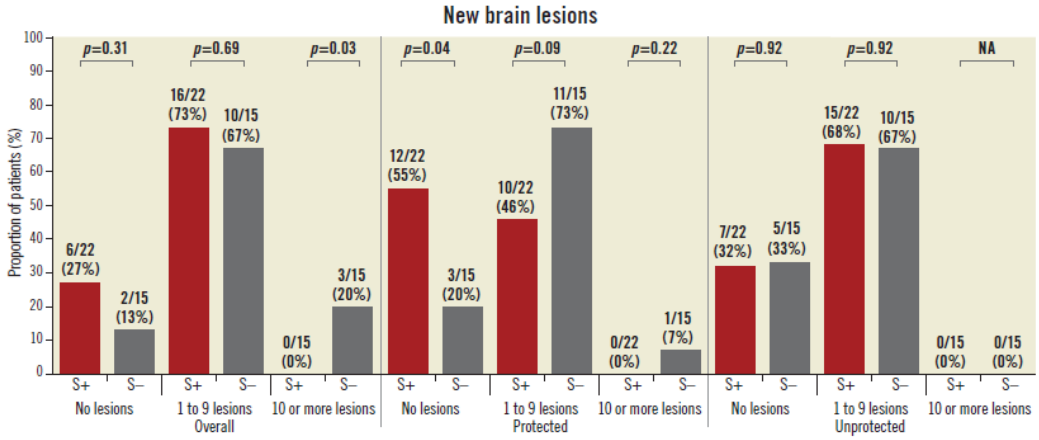

Figure 4. Occurrence and distribution of brain lesions by MRI.

a follow-up MRI for the following reasons: implantation of a non-MRI-compatible pacemaker (n=10), patient refusal (n=6), unstable clinical condition/deceased (n=5), logistical challenges (n=4) and delirium (n=3). Overall, 78% of patients with follow-up MRI had new brain lesions. There were numerically fewer new lesions and a smaller total lesion volume (95 mm3 (IQR 10-257) vs. 197 mm3 (95-525)) in patients with Sentinel CPS protection (Figure 4, Figure 5).

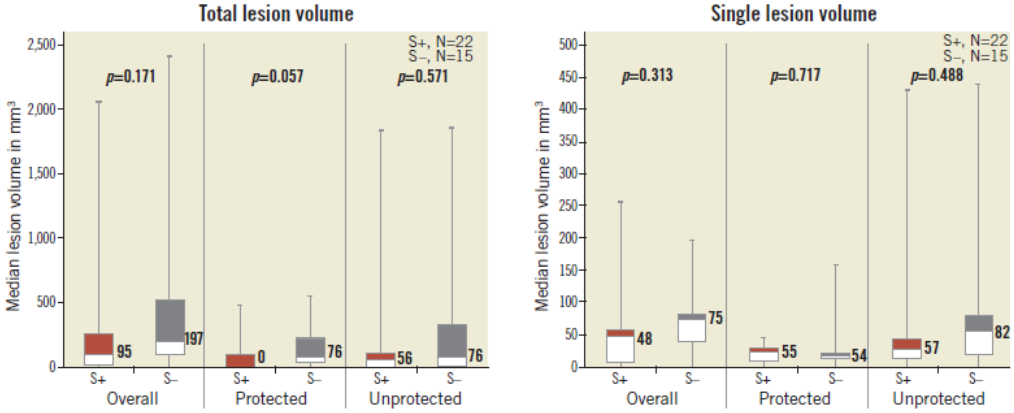

Figure 5. Brain lesion volumes at follow-up MRI. Left: overall lesion volume. Right: volume per lesion

The difference was driven by fewer lesions and smaller total lesion volume (0 mm3 (IQR 0-102) vs. 76 mm3 (IQR 40-221), p=0.057) in the protected lobes. No difference in single lesion volume was apparent (Figure 5). Overall, 27% of Sentinel CPS patients and 13% of control patients had no new lesions (Figure 4). Ten or more new brain lesions were found only in the control cohort (in 20% vs. 0% in the Sentinel CPS cohort, p=0.03). Half of the patients with Sentinel CPS protection had no new lesions in the protected lobes vs. 20% of patients without protection (p=0.04). There was no difference in the occurrence of new lesions in the unprotected lobes. Total lesion volume was greater in patients with self-expanding TAVI vs. balloon-expandable TAVI (693 mm3 (IQR 459-744) vs. 266 mm3 (IQR 155-358), p=0.067). In particular, the lesion volume in the posterior lobes was significantly greater with self-expanding THVs (405 mm3 (IQR 332-530) vs. 92 (IQR 40-240), p=0.037).

Neurocognitive performance

Neurocognitive assessment was complete for all patients at baseline and for 80% at follow-up at a mean of 5±1.0 days after TAVI. Fifteen patients did not undergo follow-up neurocognitive testing, due to logistical issues (11 cases), delirium (two cases) and clinically unstable condition (two cases). Changes in neurocognitive performance were mainly identified through MMSE. MMSE score increased by 0.25±1.6 in patients with Sentinel CPS and decreased by 0.77±2.5 in the control group (p=0.086). Neurocognitive deterioration was present in one patient (4%) with the Sentinel CPS vs. six patients (27%) without (p=0.017) (Figure 6).

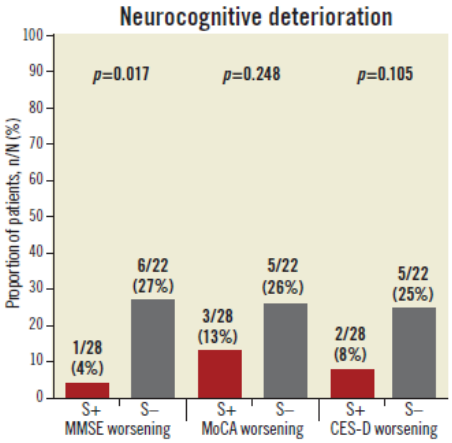

Figure 6. Relative proportion of patients with deterioration in neurocognitive performance after TAVI.

Histopathology

Debris was found in all patients who were treated with the Sentinel CPS (Figure 7). Thrombotic material and tissue-derived material were present in 87% and 100% of patients, respectively. Tissue stemmed from the myocardium, aortic valve and/or atherosclerotic arterial plaques. Foreign body polymer material stemming from catheters and valve delivery systems appeared in 30% of all patients.

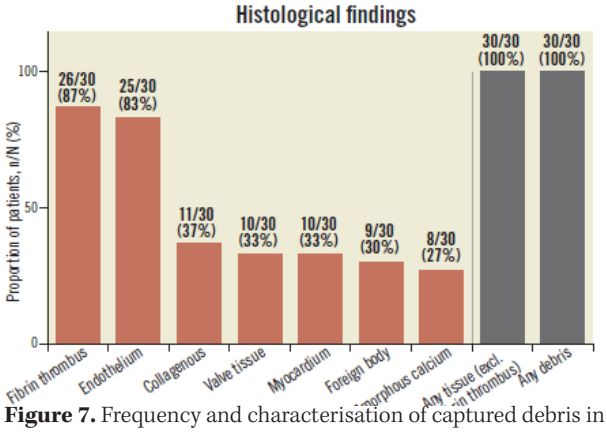

Figure 7. Frequency and characterisation of captured debris in all patients undergoing TAVI with Sentinel CPS protection.

DISCUSSION

The MISTRAL-C trial is a mechanistic study that underscores the potential value of filter-based cerebral embolic protection with TAVI. Filters capture thrombotic and/or tissue-derived debris in all patients undergoing TAVI and will result in fewer and overall smaller ischaemic brain lesions in the protected brain areas and consequently preserve neurocognitive performance.

The primary endpoint of MISTRAL-C was the presence and volume of new ischaemic brain lesions as assessed by sequential (pre- and post-TAVI) MRI. Unfortunately, compliance with follow-up MRI appeared challenging in this population of octogenarians at high operative risk. A total of 43% of patients did not complete the follow-up MRI study, mainly because of the need for PPI and patient refusal. This loss to MRI follow-up parallels the 41% and 33% in the DEFLECT III and PROTAVI trials (19,28). In MISTRAL-C, 78% of patients had new brain lesions at a median of five days after TAVI. This finding reconciles the previously reported 60-90% incidence of new brain lesions by MRI within one week after TAVI (29). The use of filter protection did reduce the total number and the total volume of lesions. These benefits clustered in the areas irrigated by the carotid arteries and seem to fit with the fact that the current Sentinel CPS version does not protect the left vertebral artery. Over a quarter of patients undergoing TAVI with Sentinel CPS protection had no new brain lesions, while half had no new lesions in the protected lobes. In the PROTAVI pilot study, all patients developed new brain lesions post TAVI and use of Embrella embolic protection (Edwards Lifesciences Ltd, Irvine, CA, USA) did not affect lesion characteristics (28). The randomised DEFLECT III trial reported freedom from ischaemic brain lesions in 21% of patients undergoing TAVI with TriGuard embolic protection and, furthermore, there were numerically fewer and smaller lesions (19). A more detailed comparison between the various MRI studies evaluating different embolic protection devices is hazardous because of MRI field strength (1.5 vs. 3 Tesla), MRI analysis methodology and because the timing of MRI follow-up after TAVI was not uniform. DWI at a higher field strength is more sensitive, can detect smaller lesions, allows shorter acquisition time and has a higher signal-to-noise ratio (18). Baseline mapping may be important to address existing lesions properly. Also, the number and size of detected lesions can change considerably within the first week post procedure. A short interval following TAVI is logistically and clinically challenging, yet longer intervals may miss transient brain injuries and new lesions may appear that are not immediately procedure-related. Kahlert et al demonstrated that 80%

of the newly acquired brain lesions by MRI at a median of 3.4 days after TAVI had resolved three months later and thus represent ischaemic but not infarcted areas (10).

In MISTRAL-C, two neurological events were described, both in patients without Sentinel CPS. This 3% disabling stroke rate fits with contemporary published TAVI data (8,30). Paired neurocognitive testing comprised three screening tests and was complete in 80% of patients. Neurocognitive performance deteriorated more often in patients without Sentinel CPS. Only the MMSE showed significant dynamic changes around the TAVI procedure. In DEFLECT III, MoCA neurocognitive testing was performed, and paired assessments with baseline were available for 88% and 74% of patients at a mean of 5.6±2.2 days and 30 days, respectively (19).

Patients who underwent TAVI with TriGuard protection appeared to have less worsening in MoCA assessment. Ghanem et al used the repeatable battery for the assessment of neuropsychological status (RBANS) in 111 patients undergoing TAVI (31). Procedural testing three days after TAVI could not be completed in 13% of patients because of critical illness, and transient early cognitive decline was detected in 6% (6/97).

Neurocognitive performance was similar to baseline at later time points up to two years. In the absence of solid guidelines, results of serial neurocognitive assessments need to be interpreted with caution. In fact, MMSE has not been developed for frequent serial testing, and changes of <2 points may still represent measurement error, regression to the mean, or a practice effect (24). The comparison of TAVI studies involving serial brain MRI and neurocognitive assessment requires caution in the absence of uniformity in the timing and methodology of these tests (18). Initiatives to harmonise further research in this field and provide guidance based on expertise and consensus are underway.

The current-generation Sentinel CPS offers filter protection to three of the four major arterial conduits to the brain, leaving the left vertebral artery unprotected. In general, the left vertebral artery is more dominant than the right vertebral artery and therefore has a larger vascular territory (32). Filter effects should therefore predominantly manifest in the vascular territory of the anterior and medial cerebral arteries. Indeed, half of all patients with Sentinel CPS protection did not have new lesions in the protected brain regions and new lesions appeared smaller. The appearance of new subclinical ischaemic brain lesions and micro infarcts may pose meaningful threats to neurocognitive function and psychosocial wellbeing in lower-risk and younger patients with symptomatic severe AS who may arguably become candidates for TAVI in the near future (22,23).

Limitations

Our study had a small sample size and was underpowered due to a higher than expected MRI drop-out rate. Also, despite randomisation, the STS score was significantly higher in patients treated without Sentinel CPS, who also had more major vascular complications. Yet, patients with major vascular complications did not complete MRI or neurocognitive follow-up and therefore did not affect our findings in terms of brain lesions and neurocognitive performance. We only assessed the early postoperative timeframe. The longer-term significance of early neurocognitive deterioration and transient ischaemic brain lesions that may not result in permanent infarcts is unsettled. The MISTRAL-C results should be considered hypothesis-generating and justify the larger randomised SENTINEL trial (NCT02214277) evaluating the Sentinel CPS that is currently recruiting patients in the USA and Germany.

Conclusion

Filter-based embolic protection captures debris en route to the brain in all patients undergoing TAVI. This study suggests that its use can lead to fewer and overall smaller new brain lesions as assessed by MRI and preservation of neurocognitive performance early after TAVI. These hypothesis-generating findings need confirmation in a larger randomised trial.

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CHAPTER XI

Complete filter-based cerebral embolic protection with transcatheter aortic valve replacement

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ABSTRACT

Objectives

To evaluate the value of left vertebral artery filter protection in addition to the current filter-based embolic protection technology to achieve complete cerebral protection during TAVR.

Background

The occurrence of cerebrovascular events after transcatheter aortic valve replacement (TAVR) has fueled concern for its potential application in younger patients with longer life expectancy. Transcatheter cerebral embolic protection (TCEP) devices may limit periprocedural cerebrovascular events by preventing macro and micro-embolization to the brain. Conventional filter-based TCEP devices cover three extracranial contributories to the brain, yet leave the left vertebral artery unprotected.

Methods

Patients underwent TAVR with complete TCEP. A dual-filter system was deployed in the brachiocephalic trunk and left common carotid artery with an additional single filter in the left vertebral artery. After TAVR all filters were retrieved and sent for histopathological evaluation by an experienced pathologist.

Results

Eleven patients received a dual-filter system and nine of them received an additional left vertebral filter. In the remaining two patients, the left vertebral filter could not be deployed. No periprocedural strokes occurred. We found debris in all filters, consisting of thrombus, tissue derived debris, and foreign body material. The left vertebral filter contained debris in an equal amount of patients as the Sentinel filters. The size of the captured particles was similar between all filters.

Conclusions

The left vertebral artery is an important entry route for embolic material to the brain during TAVR. Selective filter protection of the left vertebral artery revealed embolic debris in all patients. The clinical value of complete filter-based TCEP during TAVR warrants further research.

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is recommended in patients with symptomatic severe aortic valve stenosis (AS) and an elevated surgical risk (1–6), and is serving a growing proportion of patients (7). As with surgical aortic valve replacement TAVR comes with a 30-day major stroke rate of approximately 2–5% (8). TAVR requires large bore catheter navigation through the arterial vasculature and the implantation of a bioprosthesis within a degenerated aortic valve, which may provoke intraprocedural tissue dislodgment. Indeed, transcranial Doppler, brain magnetic resonance imaging (MRI) and histopathology studies suggest cerebral embolization in the vast majority of TAVR procedures (9–12). Silent brain lesions and (micro-) infarcts may not be trivial, as they are associated with neurocognitive deterioration (13).

Dedicated deflecting and filter-based devices were designed to reduce cerebral embolization. The DEFLECT-III trial demonstrated fewer ischemic brain lesions and preserved neurocognition with the TriGuard deflector (14). The Sentinel transcatheter cerebral embolic protection (TCEP) device (Claret medical, Santa Rosa, CA) provides filters to the brachiocephalic trunk and the left common carotid artery and thus omits the left vertebral artery. Recent studies demonstrated debris capture in almost all patients undergoing TAVR with Sentinel TCEP (15,16). Three randomized trials compared brain-MRIs several days after TAVR in patients who did receive TCEP to those who did not (16–18). None of those studies reached the primary endpoint and the efficacy of embolic protection is currently still under debate. In the CLaret Embolic Protection ANd TAVI—Trial (CLEAN-TAVI) a 57% reduction in lesion volume to the entire brain was assigned to the use of embolic protection, and a 65% reduction in protected areas only (i.e., not vascularized by the left vertebral artery) (17). Interestingly, in the randomized MRI Investigation in TAVI with Claret (MISTRAL-C) trial, the difference between reduction of lesion volume of protected regions compared to the entire brain was greater (100% vs. 48%) (18). Similarly, the cerebral protection in transcatheter aortic valve replacement (SENTINEL) trial showed a 42% reduction of lesion volume in protected territories whereas this effect was only 5% when the entire brain was considered (16). These findings suggest that debris could still embolize to the brain through the unprotected left vertebral artery. Indeed, current generation Sentinel TCEP leaves the left vertebral artery unprotected which is known to account for up to 20% of total brain perfusion (19). This hypothesis is strengthened by a study, which demonstrated that a significant number of cerebral infarcts after TAVR occur in regions that are partly vascularized by the vertebral arteries, namely the posterior lobes (33%) and the cerebellum/brainstem (27%) (20).

The Wirion (Allium Medical, Inc., Caesarea, Israel) is a single filter unit that can be delivered, locked and deployed on any commercial 0.01400 guidewire, and deployed in vessels ranging from 3.5 to 6.0 mm in diameter. The aim of this study was to evaluate whether selective Wirion deployment in the left vertebral artery would capture additional thrombotic or tissue derived debris during TAVR and as such could complement Sentinel TCEP protection.

MATERIALS AND METHODS

This prospective single-arm observational study enrolled 11 patients with severe AS from June 2014 to January 2015 in the Erasmus Medical Center in Rotterdam. All patients were deemed at high operative

risk and suitable for transfemoral TAVR by heart team consensus. All patients provided written informed consent for the procedure and data analysis for research purposes per Institutional Review Board approval.

TAVR procedures evolved under general anesthesia. All patients were preloaded with aspirin and clopidogrel and received intravenous heparin during the procedure aiming for an activated clotting time >250 s. A contrast injection in the aortic arch was performed to visualize the dimensions and position of the carotid and vertebral arteries in order to assess eligibility for both TCEP devices. The TCEP devices were inserted prior to any catheter manipulation in the aortic arch. All commercially available transcatheter heart valve designs were allowed. During the inclusion period of the study, our automated software for 3-dimensional CT reconstruction (3mensio, Pie Medical Imaging, Maastricht, The Netherlands), did not possess the functionality to assess small vessels such as the carotid arteries and left vertebral artery, yet. In 2016 a software update enabled assessment of these small vessels as well. We performed a post-hoc CT analysis to assess the aortic arch anatomy and vascular diameters and calcification.

Embolic protection technique

Figure 1 illustrates the position of the Sentinel TCEP and Wirion filter during TAVR. The Sentinel TCEP consists of two cone-shaped nitinol filters with a polyurethane film and 140 mm pores mounted on a steerable delivery catheter. The filters are integrated in a 100 cm steerable delivery system with a customized handle to articulate its distal portion. The target vessel size for the proximal filter (brachiocephalic trunk) ranges from 9 to 15 mm and for the distal filter (left common carotid artery) from 6.5 to 10 mm. The assembly is inserted through a right radial access. The proximal filter is deployed in the brachiocephalic trunk, the distal filter in the left common carotid artery. A detailed description of the deployment technique was described previously (21).

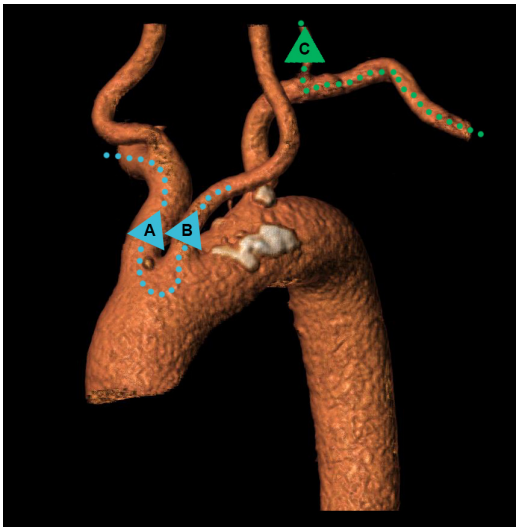

Figure 1. Reconstruction of the aortic arch illustrating the position of the filters during TAVR. One dotted line (Diamond A&B) represents the Sentinel TCEP with the proximal filter positioned in the brachiocephalic trunk (Diamond A) and the distal filter in the left common carotid artery (Diamond B). The other dotted line represents the Wirion device with the filter positioned in the left vertebral artery (Diamond C).

The Wirion contains a nitinol frame and a 120 mm pore size membrane. A dedicated delivery system with a rapid exchange (Rx) port 38 cm from its tip houses the filter unit. A dedicated activating handle can lock the filter unit onto any 0.014" guidewire. The target vessel size ranges from 3.5 to 6.0 mm.

Through a left radial approach a 0.014" guidewire is maneuvered into the left vertebral artery. The Wirion-delivery catheter is inserted onto the guidewire and advanced into the left vertebral artery under fluoroscopic guidance. The filter unit is then locked onto the wire by rotating the handle clockwise. Retracting the delivery catheter expands and deploys the filter. The Wirion is removed by advancing a dedicated

retrieval catheter over the filter unit and pulling the assembly back.

At the end of the TAVR procedure, Sentinel and Wirion filters were detached from their respective delivery system and stored in a buffered formalin (4%) solution. An experienced pathologist (MS) analysed all filters. Captured debris was dehydrated, embedded in paraffin and cut into sections of 3- to 4-mm thickness. Tissue sections were stained with hematoxylin-eosin and Movat pentachrome. Material smaller than 0.25 mm was processed using the Cellient-system and stained with both Giemsa and hematoxylin-eosin. Additional staining techniques were performed whenever applicable to identify specific tissue origin, as previously described (11).

Data management

Patient specific and procedure related data was prospectively collected and stored in a dedicated database. All patients were followed for 30 days. Relevant clinical endpoints at 30 days were categorized using the most recent Valve Academic Research Consortium (VARC) document (22).

Statistical analysis

All statistical analyses were performed with SPSS version 21.0.1 (IBM Corp, Armonk, NY). Data are presented as mean (6SD) or median (interquartile range) if continuous or as number if dichotomous. Continuous variables were compared using the Mann-Whitney-U test and a Chi-square test was used for trends in dichotomous variables. A two-sided value of $p<0.05$ was considered statistically significant.

RESULTS

Patient characteristics

Eleven patients were included in this study. Baseline characteristics are shown in Table 1. Median age was 81 and 7 patients were female. Most patients were symptomatic, 10 of 11 patients were New York Heart Association (NYHA)-class 2–4. Comorbidities were common, mean Log-EuroSCORE and STS-score were 15.7 ± 8.4 and 5.1 ± 1.7, respectively.

	N=11
Age; median, IQR	81, 78–83
Female; n	7
Body mass index in kg/m²; mean ± SD	26 ± 4
Diabetes; n	2
Hypertension; n	7
New York Heart Association (NYHA)—class; n	
I	1
II	3
III	6
IV	1
Log EuroSCORE; mean ± SD	15.7 ± 8.4
Society of thoracic surgeons (STS)-score; mean ± SD	5.1 ± 1.7
Peripheral arterial disease; n	3
Chronic obstructive pulmonary disease; n	4
Previous stroke; n	2
Previous myocardial infarction; n	3
Previous coronary artery bypass grafting; n	4
Previous percutaneous coronary intervention; n	4
Previous surgical aortic valve replacement; n	1
Carotid stenosis; n	4
Porcelain aorta; n	3

Table 1. Baseline characteristics.

	N=11
Thirty day mortality, n	0
Thirty day stroke, n	1*
New Permanent pacemaker, n	2
Conversion to surgery, n	0
Coronary obstruction, n	0
Valve embolization, n	0
Cardiac tamponade, n	0
Peri-procedural myocardial infarction, n	0
Bleeding within 24 hr, n	
Minor bleeding	2
Major bleeding	0
Life-threatening bleeding	1
Bleeding after 24 hr, n	
Minor bleeding	5
Major bleeding	0
Life-threatening bleeding	0
Vascular complication, n	
Minor vascular complication	6
Major vascular complication	2
Access site related vascular complication, n	6

Table 2. VARC-II endpoints. *Patient had an ischemic stroke 8 days after the TAVI procedure.

Two patients previously underwent a cerebral stroke and four patients had a known carotid stenosis. Three patients had a porcelain aorta.

Procedural characteristics

Eight patients underwent TAVR with the Lotus valve (Boston Scientific, Marlborough, MA), two patients with a Sapien 3 valve (Edwards Lifesciences, Irvine, CA), and one patient with a CoreValve (Medtronic, Minneapolis, MN). Median fluoroscopy time was 27.4 min (IQR 23.3–35.5). Median anesthesia time (i.e., time on catheterization laboratory) was 212 minutes (IQR 190–214). Median contrast load was 110cc (IQR 80–150).

Sentinel TCEP was successfully deployed in all patients. In two of eleven patients the implantation of the Wirion-filter was unsuccessful due to the following reasons: In one patient we were unable to advance a guidewire into the left vertebral artery due to anatomical difficulties and in one patient we caused a dissection of the left vertebral artery. The latter was treated with a stent. We excluded these patients from our histopathological analysis.

Clinical endpoints

Clinical outcomes are displayed in Table 2. None of the eleven patients died during the first month of follow-up. There were no events of coronary obstruction, valve embolization or cardiac tamponade. Conversion to surgery did not occur. One patient experienced a life-threatening gastro-intestinal bleeding within 24 hr after the procedure. This same patient developed an ischemic stroke on the 8 days after the procedure. One major vascular complication resulted from the introduction of the Wirion-device into the left vertebral artery, which was previously mentioned. Six patients experienced a minor vascular complication related to the femoral access site. In five cases there was a hematoma at the femoral puncture site and one patient had a dissection of the femoral artery, which was treated with a covered stent.

Histopathological analysis

In total, 31 filters were retrieved: 11 originating from the brachiocephalic trunk (Sentinel first filter), 11 from the left common carotid artery (Sentinel second filter), and 9 from the left vertebral artery (Wirion filter). The histopathological analysis revealed that all filters contained debris. An overview of the retrieved contents is shown in Figure 2. Fibrin/trombus was the most frequently seen element, which was found in the Sentinel TCEP filters in all patients and in seven of nine Wirion filters. When fibrin/trombus was not taken into account, Sentinel and Wirion filters all contained tissue material. Endothelium was the most commonly found tissue (Sentinel 9/11 patients vs. Wirion 7/9 patients). Apart from endogenous tissue, foreign body material was also detected in the majority of patients (Sentinel 6/11 patients vs. Wirion 6/9 patients). This foreign body material consisted of blue gel or colored fibers, likely derived from catheters or the TAVR delivery system. No differences were observed between the Sentinel and Wirion filter for any type of debris.

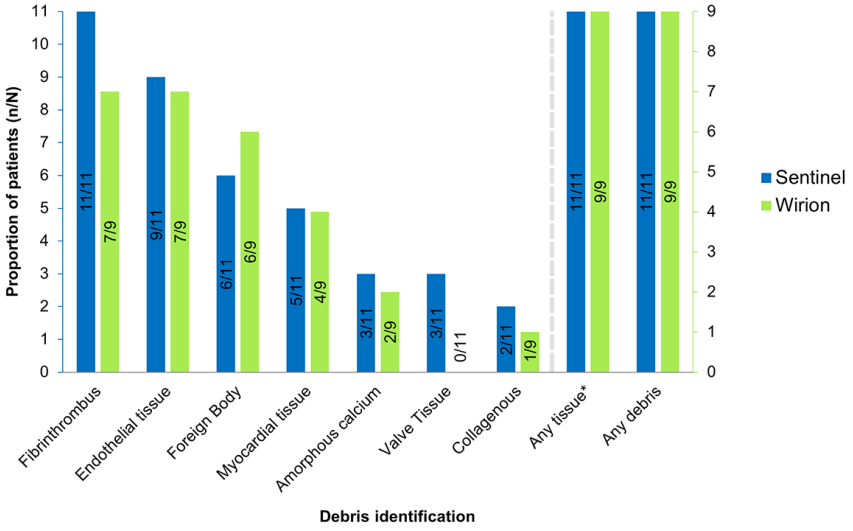

Figure 2. Graph illustrating distribution of embolic debris in Sentinel and Wirion filters. *Presence of tissue fragments excluding thrombus tissue.

Tissue size

Concerning the size of the debris, the largest particles consisted of amorphous calcium in both the Sentinel and Wirion filters with a median diameter of 0.60 and 0.33 mm, respectively (Figure 3). There were no differences in the median diameter for each tissue type between the Sentinel and Wirion filters.

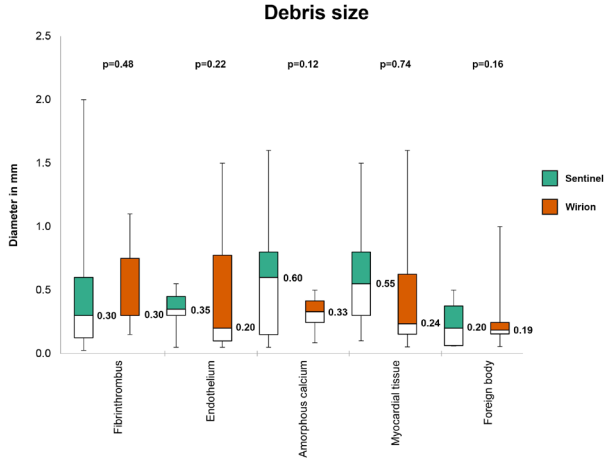

Figure 3. Boxplots displaying median size (minimum -Q1-median-Q3-maximum) per tissue type for debris from Sentinel and Wirion filters.

CT analysis

Results from the post-hoc CT analysis are displayed in Table 3. Aortic arch anatomy was normal in 8 of the 11 patients, two patients had a bovine arch and one patient had an anomalous origin of the left vertebral artery. All dimensions of the brachiocephalic trunk, left common carotid artery and left vertebral artery were within the range of the manufacturers' instructions for use. Three patients had at least moderate calcification of the brachiocephalic trunk and left common carotid. Also, three patients had at least moderate calcification of the left vertebral artery, of which two had no calcifications in the brachiocephalic trunk of left common carotid artery, whatsoever.

	N=11
Aortic arch anatomy	
Normal	8
Bovine	2
Left vertebral arises from arch	1
Brachiocephalic trunk average diameter in mm; median, IQR	12.7 (11.0–13.4)
Left common carotid artery average diameter in mm; median, IQR	7.1 (6.7–8.0)
Left vertebral artery average diameter in mm; median, IQR	4.0 (3.5–4.4)
Brachiocephalic trunk calcification	
None	7
Mild	1
Moderate	3
Severe	0
Left common carotid artery calcification	
None	7
Mild	1
Moderate	3
Severe	0
Left vertebral artery calcification	
None	5
Mild	3
Moderate	2
Severe	1

Table 3. Computed tomography findings.

As mentioned above, in two of the eleven patients the implantation of the Wirion filter was unsuccessful. The first was the patient with the anomalous origin of the vertebral artery. The second was the patient with the severely calcified vertebral artery in which a dissection was caused by the guidewire.

DISCUSSION

This study reveals that both the amount and size of debris that passes through the left vertebral filter during TAVR is comparable to the amounts that passes through the brachiocephalic trunk and left common carotid artery. Currently available filter-based TCEP only includes the brachiocephalic trunk and left common carotid artery (21). Our study indicates that protection of three out of four extracranial arterial contributors offers incomplete brain protection.

A study by Arnold et al. demonstrated lesion frequency on MRI after transapical TAVR without embolic protection (20). The authors concluded that 17 of the 25 patients (68%) had new embolic lesions, of which six had more than five lesions. This is in line with previous studies that reported brain MRI findings after TAVR (9,10,23,24). Interestingly, 27% of the lesions was localized in the cerebellum and brainstem (27%)

of which the vertebral arteries is a large vascular contributor. A study by Kahlert et al. reported 29% of new lesions in the vertebro-basillary region after transfemoral TAVR (9). Both studies did not differentiate between the left and right vertebral artery. A study by Ghanem et al. reported that ≈12% of cerebral lesions is located in the region that is particularly vascularized by the left vertebral artery (10), and a study by Astarci et al. reported a number as large as ≈17% in this region (24). Of note, these are probably underestimations since the vascular territories of the posterior cerebral arteries and vertebral arteries largely overlap. In conclusion, these four studies are in line with previous findings that indicated the left vertebral artery accounts for up to 20% of blood flow to the brain (19).

Previously, we reported the embolic load that was captured with the Sentinel TCEP (11). This study showed that 75% of patients had some amount of debris in the filters. In both the MISTRAL-C and SENTINEL trials debris was captured in ≈100% of patients (16,18). This study showed debris in all filters too. Both self-expanding and balloon expandable valve designs have been studied in earlier studies (16,18). In this study, eight patients were treated with the mechanically expanded Lotus valve, two with the balloon expandable Sapien 3 and 1 with the self-expanding CoreValve.

In our study fibrin/trombus, endothelial tissue and foreign body material were frequent. The debris size in the Sentinel TCEP filters of 0.05–1.6 mm and in the Wirion filters of 0.05–1.6 mm is similar to what we reported earlier (11). Interestingly, myocardial tissue was captured in more than half of the patients and compares with the 33% reported in the MISTRAL-C and 16% in SENTINEL trials. It indicates that TAVR induces myocardial tissue damage due to traumatic contact with the introduced catheters or delivery system.

The additional use of the Wirion filter had minimal implications on the TAVR procedure itself. The total fluoroscopy time of 27.4 min was comparable with usual TAVR standards (25), as was the anesthesia time or 212 min (26). Use of contrast was modest with 110 ml per procedure, and in keeping with other studies (27). The Wirion filter is easy to advance over a genuine coronary 0.014" guidewire and its deployment is intuitive. However the take-off and trajectory of the left vertebral artery may be challenging and might preclude safe negotiation. In two patients we were unsuccessful to deploy a Wirion filter selectively into the left vertebral artery and even generated a vascular complication that required stenting. Sub-selective filter deployment in the subclavian artery distal to the origo of the left vertebral artery may be a safer landing zone. In addition, pre-procedural CT analysis of the carotid and vertebral arteries with dedicated software (that became available to us in 2016) might be helpful to select those patients who are eligible for embolic protection filters. In this small pilot study, the post-hoc CT analysis was able to show that the two patients in which the deployment of the left vertebral filter was unsuccessful had an unfavorable anatomy beforehand. In our experience, pre-procedural planning using multiplanar CT reconstructions has become a prerequisite for both the TAVR procedure itself as the use of embolic protection.

In our relatively small study population of eleven patients, none experienced a periprocedural stroke. One patient underwent a stroke on the eight day after TAVR after two episodes of cardiopulmonary resuscitation for total atrioventricular block.

Since periprocedural stroke occurs seldom after TAVR previous studies have been underpowered to reveal a benefit of embolic protection on this endpoint. Therefore, studies focused on softer endpoints such as lesion volume by brain-MRI. Three randomized trials investigated the benefit of TCEP by brain-MRI

several days after TAVR. First, the CLEAN-TAVI study randomized 100 patients to either TAVR with or without TCEP and 88 patients underwent a brain-MRI at 7 days (17). The lesion volume in the entire brain was reduced by 57% (205 mm^3 vs. 472 mm^3, p=0.009) with use of TCEP, and 65% (101 mm^3 vs. 292 mm^3, p=0.002) in the protected areas. Second, the MISTRAL-C study randomized 65 patients of which 37 underwent brain-MRI at 5 days (18). Total lesion volume in the entire brain was reduced by 48% (95 mm^3 vs. 197 mm^3, p=0.171) and by 100% (0 mm^3 vs. 76 mm^3, p=0.057) in the protected lobes. Third, the SENTINEL study randomized 240 patients of which 185 underwent brain-MRI between day 2 and 7 (16). Total lesion volume in the entire brain was reduced by 5% (294 mm^3 vs. 310 mm^3, p=0.81), and by 42% (103 mm^3 vs. 178 mm^3, p=0.33) in the protected territories. Although these studies were likely underpowered to show a significant reduction in lesion volume all studies point toward a greater reduction in the protected regions compared to the entire brain. This strengthens the hypothesis that protection of the left common carotid and brachiocephalic trunk might be suboptimal.

It will be hard to demonstrate a clinical benefit of complete over incomplete filter protection, therefore future studies should focus on surrogate endpoints such as lesions on brain-MRI or neurocognitive performance, as proposed by a recent academic research consortium consensus document (28).

Limitations

This prospective single arm study was intended to reveal whether protection of the left vertebral artery could be beneficial in TAVR. The study was small, and should therefore be considered hypothesis generating. Post-procedural brain imaging was not performed and we acknowledge that this should be a target for future studies to investigate the benefit of left vertebral artery protection during TAVR.

CONCLUSION

This study, involving first in human complete filter-based TCEP during TAVR confirms that the left vertebral artery is relevant entry route for embolic material toward the brain. No periprocedural strokes occurred during 30-day follow up. More evidence is needed to support beneficial effects of TCEP over existing strategies.

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CHAPTER XII

Cerebral embolic protection in catheter-based mitral interventions. Research or clinical tool?

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Transcatheter MitraClip (Abbott Vascular, Santa Clara, California) implantation has emerged as the single catheter-based technique for mitral valve repair with global adoption. Worldwide, an estimated 25,000 patients have been treated with the MitraClip so far. Typically, the incidence of major stroke after surgical mitral valve repair or replacement is similar to what is seen after surgical aortic valve replacement, and varies between 1% and 5% (1–3). In the only randomized trial comparing MitraClip with mitral valve repair/ replacement, major stroke rate at 30 days was 1% after MitraClip and 2% after mitral valve surgery (4). The EVEREST (Endovascular Valve Edge-to-Edge Repair Study) 2 predominantly enrolled patients with degenerative mitral valve disease (4). In the larger European MitraClip registries, patients had more functional mitral regurgitation (MR). The clinically major stroke rate after clipping appeared to be negligible and <1%: 0.7% in 560 patients in the ACCESS EU (ACCESS-Europe A Two-Phase Observational Study of the MitraClip System in Europe) trial, and 0% in 1,064 patients in the German TRAMI (Transcatheter Mitral Valve Interventions) Registry (5,6).

Important lessons were learned after a decade of controversy about stroke rates in patients undergoing surgical or catheter-based aortic valve replacement. The randomized PARTNER (Placement of Aortic Transcatheter Valve) I trial seemed to suggest that the less-invasive transcatheter aortic valve replacement (TAVR)was associated with a higher neurological event rate compared with surgical aortic valve replacement; yet, the randomized U.S. CoreValve high-risk study refuted these findings (7,8). Interestingly, the involvement of competent authorities like the U.S. Food and Drug Administration, efforts by the Valve Academic Research Consortium to determine uniformity in endpoint definitions and trial design, and the advent of embolic protection devices have scrutinized research on neurological events in the field (9). Neurology experts are now involved in most important TAVR trials and assess all enrolled patients undergoing valve replacement before and after the procedure. This scrutiny has revealed more (subtle) neurological changes in significantly more patients. Indeed, new neurological events were detected in 15% of patients in the control arm of the randomized DEFLECT III (A Prospective, Randomized Evaluation of the TriGuard HDH Embolic Deflection Device During TAVI) trial and in 17% of patients undergoing surgical aortic valve replacement in the DeNOVO (Determining Neurologic Outcomes from Valve Operations) prospective cohort study (10,11). Diffusion-weighted magnetic resonance imaging (MRI) studies and histopathology studies have revealed signs of cerebral embolization in over 80% of patients undergoing TAVR (12–14).

Deflecting and filter-based embolic protection devices (EPDs) are being intensely studied in the field of TAVR, and not surprisingly, interest for EPD also emerges in the MitraClip space (15). In this issue of JACC: Cardiovascular Interventions, Frerker et al. (16) study the use of filter-based embolic protection in patients undergoing MitraClip implantation.

The Sentinel EPD (Claret Medical Inc., Santa Rosa, California) provides filter protection for 3 of 4 arterial contributories to the brain. The filters can be retrieved and microscopically analyzed. Fourteen patients with severe MR were included in the analysis. Most patients had functional MR and concomitant permanent atrial fibrillation. Debris was detected in all patients. Acute thrombus and foreign body material was most common. The presence of acute thrombus is remarkable, especially since optimal per-procedural anticoagulation with heparin was achieved (mean activated clotting time 289 ± 48 s). This raises the question about the etiology of this acute clot formation: device manipulations in the left side of the heart but also the use of the filters themselves may be pro-thrombogenic. Furthermore, procedure times exceeding

90 min may result in transient suboptimal anticoagulation and, thus, promote acute thrombus formation. In fact, MitraClip procedure/device time has previously been associated with more new brain lesions by MRI (17). Conversely, the presence of organizing thrombus in the filters may be associated with the high prevalence of atrial fibrillation that hypothetically may have accounted for the organized thrombus surrounding the mitral valve apparatus. The authors describe the foreign body material as nonpolarizable basophilic material consistent with hydrogel, most probably from the hydrophilic coating of the transseptal sheath, guide delivery catheter, or the clip delivery system and thus inherent to the procedure. In more than one-half of the patients, mitral valve and atrial tissue was found. The authors do not discuss the effect of the number of attempts to grasp both mitral leaflets to eventually close and deploy the MitraClip. One can only wonder whether more attempts could dislodge more tissue. Furthermore, would there be a difference between functional and degenerative MR, with the latter displaying an excess of tissue? The finding that the use of more clips seemed to generate larger debris is intriguing.

In comparison to what typically is captured after TAVR, debris seemed smaller with MitraClip: 295 mm (interquartile range: 104 to 509 mm) versus 1 mm (interquartile range: 0.6 to 1.5 mm) (14). Smaller particle size may reflect the preponderance of functional MR in this study with structurally normal mitral valve leaflets. Similarly, this may explain why no calcium particles were captured. This contrasts with the yield after TAVR, with tissue debris in two-thirds of all patients including amorphous calcium.

The current data are complementary to the recent brain MRI study by Blazek et al. (17), in which a median of 3 new brain lesions were found in 85% of patients after MitraClip.

Given the (very) low clinical stroke rates after MitraClip, purists may claim that EPDs are useless in this setting. Others may argue that even subclinical brain infarcts may not be harmless and may increase the risk for dementia and neurocognitive deterioration in the long run (18). Future research efforts may focus on: 1) the difference in cerebral embolization between functional and degenerative MR; 2) the effect of EPD on new brain lesions by MRI; 3) cerebral embolization burden with transcatheter mitral valve implantation, which intuitively seems more traumatic than MitraClip and may thus dislodge more tissue debris; and maybe most importantly, 4) the effect of new brain lesions after structural heart interventions on immediate and late neurocognitive performance.

In aggregate, cerebral embolization seems ubiquitous with structural left-sided heart interventions. The study by Frerker et al. (16) provides complementary histopathological evidence to prior brain imaging data. Only the future can tell whether filter-based cerebral embolic protection is merely an interesting research tool or an essential clinical accessory for superior procedural (brain) safety.

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Interlude

CHAPTER XIII

Early stentframe thrombosis complicating transcatheter valve in transcatheter valve implantation

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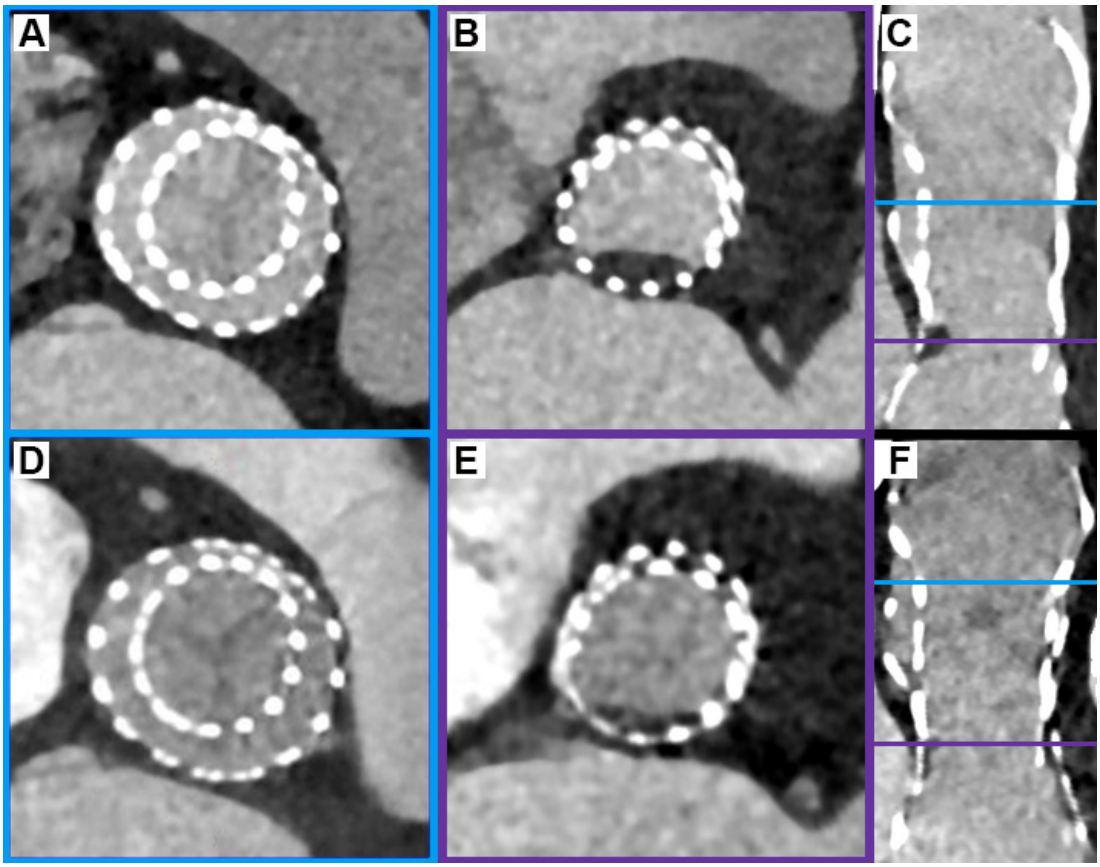
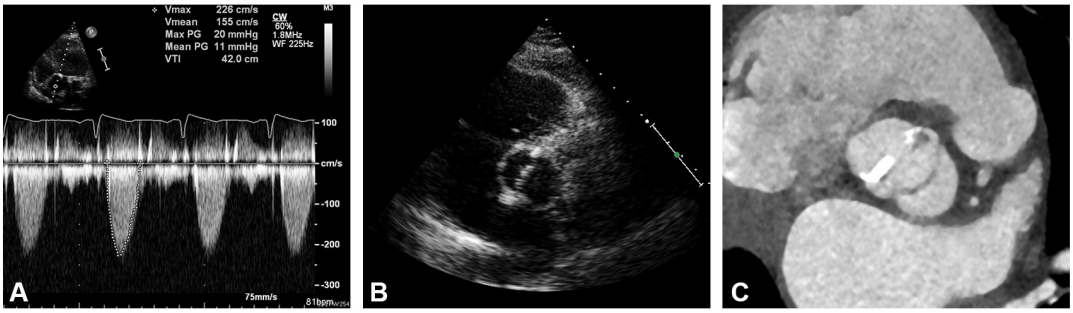
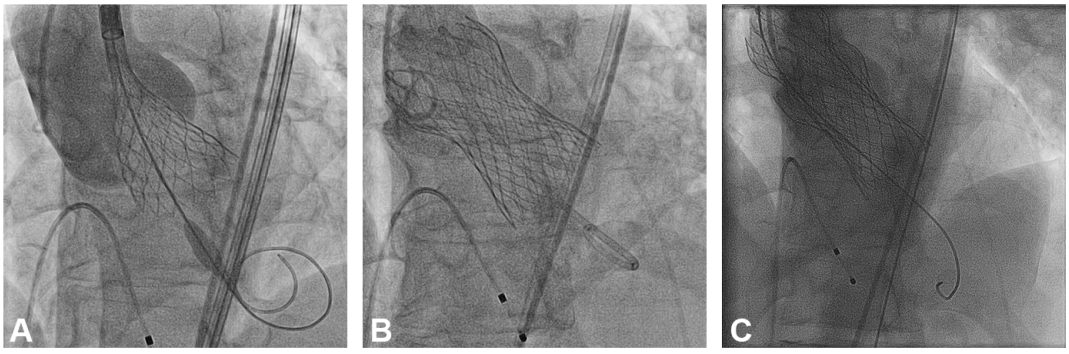
A 62-year-old woman underwent transcatheter aortic valve implantation (TAVI) for severe low-flow low-gradient stenosis of a bicuspid aortic valve (Supplemental Figure 1). She was declined for open heart surgery because of severe left ventricular dysfunction. The TAVI procedure was performed under local anesthesia and full anticoagulation with heparin and preloading with aspirin and clopidogrel. Following balloon aortic valvuloplasty, a 29 mm Core-Valve Evolut R bioprosthesis (Medtronic, Minneapolis, MN, USA) was attempted. Its deployment was associated with immediate haemodynamic compromise complicating the valve positioning and resulting in a deep implant with residual significant paravalvular aortic regurgitation (AR). A second Evolut R was implanted more cranially with complete resolution of the AR (Supplemental Figure 2). The patient was discharged home with daily aspirin and clopidogrel after an uneventful hospital stay. A planned multi-phasic CT (MSCT) scan after 30 days revealed a large thrombus (13 6 mm) at the interface of the two bioprostheses (Panel B: cross-sectional; Panel C: longitudinal). The patient was put on oral anticoagulation therapy with coumadins (acenocoumarol). MSCT scan 4 months later confirmed almost complete resolution of the stentframe thrombus. The bioprosthetic leaflets appeared slim and mobile and there were no signs of residual stenosis at 1 month after TAVI (Figure 1: Panel A) and after 4 months of subsequent oral anticoagulation therapy (Figure 1: Panel D) (Figure 1: Panel E: cross-sectional; Figure 1: Panel F: longitudinal). This case illustrates a novel phenomenon of unequivocal thrombus formation at the stent frame level without affecting the leaflets that almost completely resolved after 4 months of anticoagulation therapy. Its true incidence is unknown and requires further research. TAVI operators and treating physicians need to be aware of this entity especially in a situation of transcatheter valve-in-transcatheter-valve implantation' in combination with low-flow and low-gradient AS.





Supplemental figure 1. TTE confirmed a classical low-flow low-gradient aortic stenosis (A) of a bicuspid valve (B). Bicuspidy was also confirmed on MSCT (C).



Supplemental figure 2. Procedural angiograms before release of the first valve – depth 9 mm (A), after release of first valve – depth 20 mm (B) and after TAV-in-TAV (C).

CHAPTER XIV

Transcatheter mitral valve implantation in a patient with an aortic mechanical valve

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JACC Cardiovasc Interv. 2016 Feb 22;9(4):e31-3

A73-year old man presented with acute cardiac decompensation due to severe degenerative mitral regurgitation (Figures 1A and 1B). The patient previously underwent surgical aortic valve replacement with a mechanical valve. The patient was declared inoperable by heart team consensus based on excessive comorbidities. After staged left main bifurcation rotablation and stenting (Figures 1C and 1D), the patient was accepted for transapical transcatheter mitral valve implantation (TMVI) with the CardiAQ transcatheter heart valve (Edwards Lifesciences, Irvine, California) (Figure 2A) under compassionate use. Pre-procedural imaging work-up confirmed eligibility for the procedure in terms of overall anatomy and sizing. Relative orientation of the aortic mechanical valve and its distance to the mitral annular plane were deemed reassuring (Figures 1E and 1F). The procedure was supported by fluoroscopic and transesophageal echocardiography guidance. Through a left lateral minithoracotomy, the CardiAQ valve was smoothly navigated over a stiff guidewire into the mitral annulus and gradually deployed, with no residual mitral regurgitation on transesophageal echocardiography (Figure 2D). Final release was quickly followed by hemodynamic compromise due to massive aortic regurgitation (Figure 2E) caused by 1 immobile leaflet of the aortic mechanical valve (Figure 2F). Despite extracorporeal cardiopulmonary support and multiple bail-out transcatheter maneuvers, the patient succumbed to intractable cardiogenic shock. Autopsy revealed anatomically correct placement and sealing of the CardiAQ valve (Figure 2G). Despite excessive preprocedural planning, 2 anchors of the CardiAQ valve eventually interfered with the aortic mechanical valve (Figures 2H and 2I). As previously described, the inherent radial force needed to anchor the stented valve might squeeze the left ventricular outflow tract (1,2). This case demonstrates that the left ventricular outflow tract is an essential yet dynamic anatomic structure for TMVI, especially in the case of an aortic mechanical valve. Proper understanding of the mitral valvular anatomy is crucial for the clinical implementation and further refinement of TMVI. We believe that the presence of an aortic mechanical valve currently is a formal contraindication for TMVI.

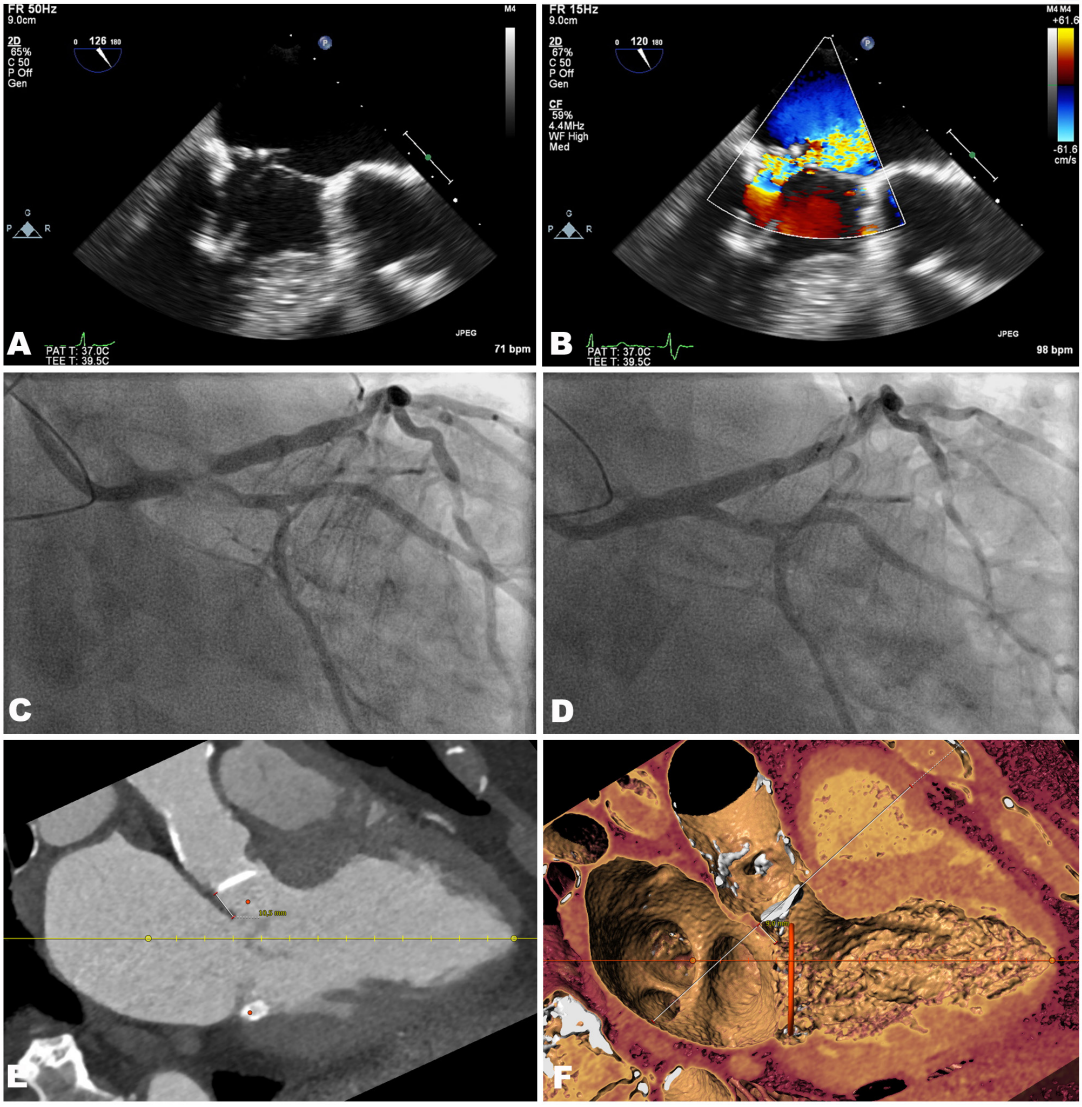

Figure 1. Pre-procedural work-up. (A) Baseline transesophageal echocardiography (TEE) showing flail of the mitral valve posterior leaflet. (B) Baseline TEE showing significant mitral regurgitation. (C) Fluoroscopic image of left main stem stenosis. (D) Fluoroscopic image of left coronary artery after main stem rotablation and stenting. (E) Pre-procedural multislice computed tomography (CT) image showing measured distance from mitral annulus to aortic mechanical valve. (F) Pre-procedural 3-dimensional reconstruction of multislice CT showing anatomic dimensions.

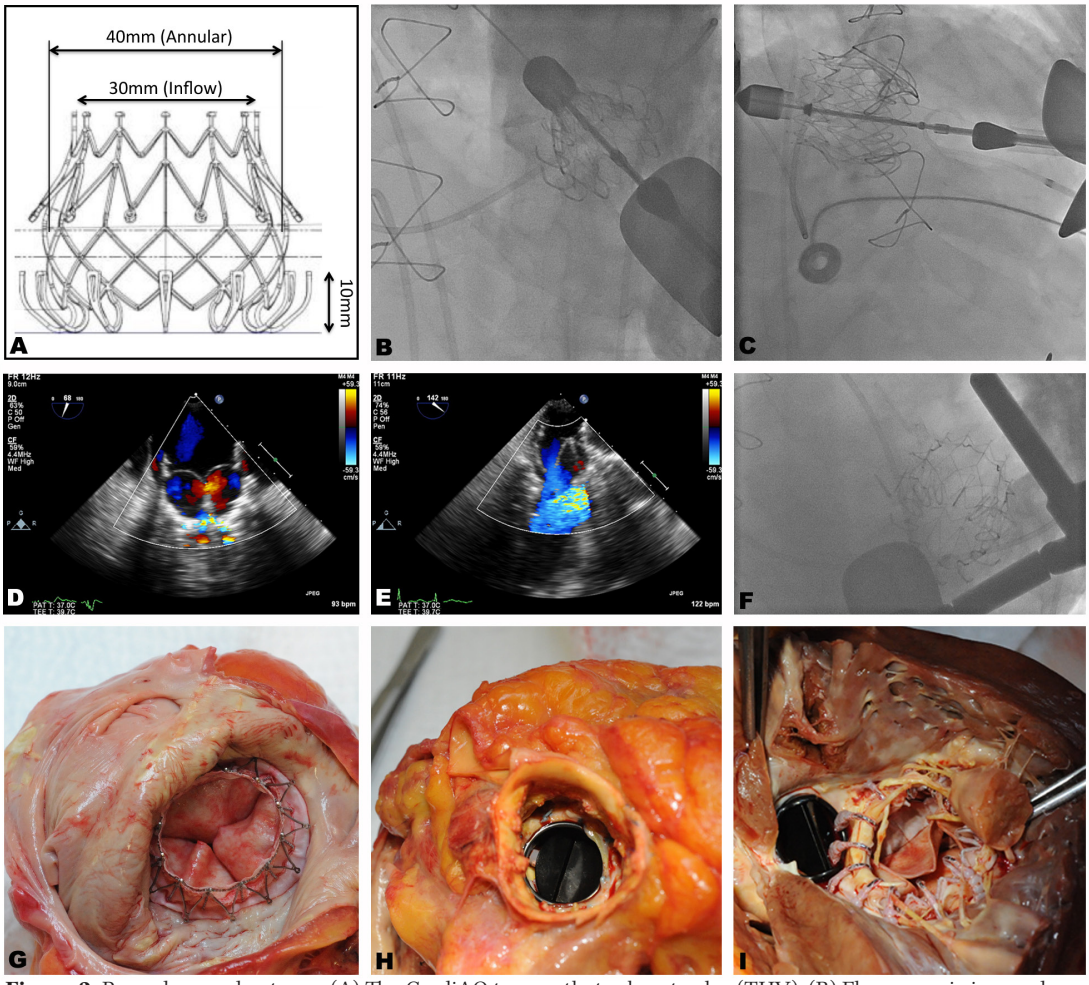

Figure 2. Procedure and autopsy. (A) The CardiAQ transcatheter heart valve (THV). (B) Fluoroscopic image during implantation of the THV. (C) Fluoroscopic image of CardiAQ THV directly after release. (D) Transesophageal echocardiography (TEE) showing absence of mitral regurgitation. (E) TEE showing massive aortic regurgitation. (F) Fluoroscopic image of interference between the aortic mechanical valve and the CardiAQ THV. (G) Autopsy photograph showing correct placement of CardiAQ THV, seen from the left atrium. (H) Autopsy photograph with visible anchor from the CardiAQ THV, seen from the ascending aorta. (I) Autopsy photograph showing 2 anchors of the CardiAQ THV interfere with the aortic mechanical valve, seen from the left ventricle.

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Part IV
Procedural planning

CHAPTER XV

Relation between calcium burden, echocardiographic stent frame eccentricity and paravalvular leakage after corevalve transcatheter aortic valve implantation

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ABSTRACT

Aims

Paravalvular aortic leakage (PVL) after transcatheter aortic valve implantation (TAVI) is a complication with potentially severe consequences. The relation between native aortic root calcium burden, stent frame eccentricity and PVL was not studied before.

Methods and results

Two-hundred-and-twenty-three consecutive patients with severe aortic stenosis who underwent TAVI with a Medtronic CoreValve System VC and who had available pre-discharge transthoracic echocardiography were studied. Echocardiographic stent inflow frame eccentricity was defined as major–minor diameter in a short-axis view >2 mm. PVL was scored according to the updated Valve Academic Research Consortium (VARC-2) recommendations. In a subgroup of 162 (73%) patients, the calcium Agatston score was available. Stent frame eccentricity was seen in 77 (35%) of patients. The correlation between the Agatston score and stent frame eccentricity was significant ($q = 0.241$, $P = 0.003$). Paravalvular leakage was absent in 91 cases (41%), mild in 67 (30%), moderate in 51 (23%), and severe in 14 (6%) cases. The correlation between stent frame eccentricity and PVL severity was significant ($q = 0.525$, $P < 0.0001$). There was a relation between particular eccentric stent frame shapes and the site of PVL.

Conclusion

Calcification of the aortic annulus is associated with a subsequent eccentric shape of the CoreValve prosthesis. This eccentric shape results in more PVL, with the localization of PVL related to the shape of stent frame eccentricity.

INTRODUCTION

Paravalvular aortic leakage (PVL) after transcatheter aortic valve implantation (TAVI) is a complication with potentially severe consequences (1,2). In particular in a self-expandable system such as the CoreValve System©, calcified valves may pose resistance to prosthesis deployment, resulting in an ellipsoid-shaped valve stent and a higher incidence of PVL. Indeed, quantification of calcification by the Agatston score was predictive for PVL in patients who underwent a CoreValve implantation (3-5). However, in CoreValve specific studies the relationships between the Agatston score and stent frame eccentricity and stent frame eccentricity vs. PVL severity and localization were not studied. Only for the balloon-expandable Edwards SAPIEN™ prosthesis, data on the correlation between stent frame eccentricity and PVL were reported by one single centre (6,7). Unfortunately, discrepant findings were reported by the authors. No relation was seen when eccentricity was assessed by transoesophageal echocardiography(7) whereas a positive relation was seen when eccentricity was defined by computed tomography (CT) (6). This study sought to assess in a large single-centre consecutive CoreValve series the relation between the Agatston score and native annulus shape vs. stent frame eccentricity, and stent frame eccentricity and subsequent PVL as defined by Valve Academic Research Consortium (VARC-2) criteria (8).

METHODS

Included in the study were 223 consecutive patients with severe aortic stenosis (AS) who underwent TAVI with a Medtronic CoreValve System VC from June 2006 to November 2012 and had pre-discharge transthoracic echocardiography. 53% of the patients were male, with a median age of 81 (78–85) years. The median logistic euroSCORE was 13 (10–21). The mean aortic pressure gradient was 42 ±17mmHg, and the mean valve area was 0.7± 0.2 cm². The TAVI implantation procedure in the Thoraxcenter is described in full detail elsewhere (9,10).

Echocardiographic study

At the time of hospital discharge, on average 6± 3 days after TAVI, the patients were evaluated using an iE33 ultrasound system (Philips Medical System, Best, TheNetherlands) equipped with a S5-1 transthoracic transducer. The extent of PVL was assessed according to VARC-2 criteria (8). PVL was measured as a continuous value as well as a categorical value: less than 10% of the circumference was defined as mild, between 10% and 30% as moderate, and more than 30% as severe PVL. The localization of PVL was assessed by dividing the stent circumference into twelve equal sectors according to a clock model. As seen in Figure 1, the native commissure

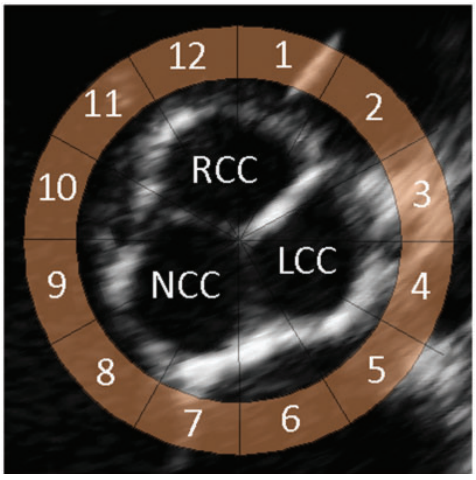

Figure 1. PVL localization was assessed by dividing the stent circumference into twelve equal sectors according to a clock model. The native commissure between the right and left cusps is located in segments 1 to 3, the one between left and non-coronary cusps in segments 5 to 7, and the one between the right and the non-coronary cusps is located in segments 9 to 11. LCC, left commissural cusp; NCC, non commissural cusp; RCC, right commissural cusp.

between the right and left cusps (RLC) is located in segments 1 to 3, the one between left and non-coronary cusps (LNC) in segments 5 to 7, and the commissure between the right and the non-coronary cusps (RNC) is located in segments 9 to 11.

The minimum and maximum diameters of the stent were also recorded in the parasternal short axis view in a mid-to-late diastolic frame, at the same stent level where PVL was measured; stent inflow frame eccentricity was defined as a difference between the maximum and the minimum diameter larger than 2mm. The non-eccentric stents were further labelled as truly circular, with identical minimum and maximum diameters, and near circular, with a difference between the diameters up to 2mm. The stents found to be eccentric were further divided in different categories following the orientation of the longest diameter in the short-axis view. As seen in Figure 2, the wide (W) shape was defined as horizontally orientated with the longest diameter between 67.5 and 112.5 degrees, the zero degree being on the upper part of the circumference; the height (H) shape as a vertically orientated longest diameter (between –22.5 and +22.5); the right (R) oblique shape with an upper right–lower left position (the longest diameter between 22.5 and 67.5 degrees); and the left (L) oblique shape with an upper left–lower right position (between 112.5 and 157.5 degrees). Finally, the echocardiographic eccentricity index was defined as 100 x (1–(minimum stent frame diameter/maximum stent frame diameter)).

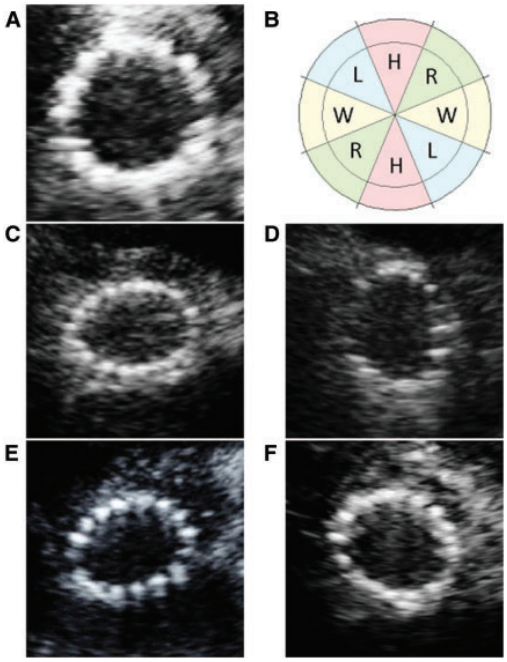

Figure 2. Example of the different stent frame shapes. A=Circular, C=Wide ('W'), D= Height ('H'), E= Right oblique ('R'), F= Left oblique ('L'). In B, the definition of shapes is explained according to the orientation of the major axis of the stent frame.

CT study

CT data were available in a subgroup of 162 (73%) patients. The assessment of the aortic annulus was performed using dual source CT (Somatom Definition, Siemens Medical Solutions, Forchheim, Germany). The pitch was adjusted to fit the heart rate. After a non-contrast scan, performed to obtain the Agatston calcification score, 50–60mL of VisipaqueVR 320 mg I/mL, (GE Health Care, Eindhoven, The Netherlands) was injected in an antecubital vein at a flow rate of 5.0mL/s followed by a second contrast bolus of 30–40 at 3.0mL/s. The scan ranged from the top of the aortic arch to the diaphragm. 3D reconstructions in end-systole were then derived using a single-segmental reconstruction algorithm with slice thickness 1.5mm and increment 0.4mm. The radiation doses ranged from 8 to 20 mSv depending on body habitus and table speed, the vast majority received radiation doses between 8 to 12 mSv. The shape of the native annulus was assessed by the eccentricity index, defined as 100 x (1–(minimum aortic annulus diameter/maximum aortic annulus diameter) (11).

Statistical analysis

All data were analysed using SPSS (IBM, version 20). Continuous variables were checked for normality of distribution via the Kolmogorov–Smirnov test and were expressed as mean (± standard deviation) or median (interquartile range). Categorical data is presented as frequency (percentage). Correlations were evaluated using the Spearman's coefficient (q). Statistical differences between groups were assessed using the Mann–Whitney and Kruskal–Wallis tests for nonparametric data.

RESULTS

Stent eccentricity

The distribution of the various stent inflow frame shapes at predischarge echocardiography is reported in Table 1. Most of the stents were circular or near-circular (difference between minor and major axis of stent frame ≤2mm) (146; 65%). Among the non-circular ones, the W shape accounted for 24 cases (11%), the H shape for 11 (5%), the R shape for 25 (11%), and the L shape for 17 (8%).

Shape category	Patients	VARC-2 score	P-value vs. circular shape
Circular	146 (65%)	4% (±7%)	
Truly circular	43	1% (±5%)	
Near-circular	103	5% (±8%)	
Eccentric	77 (35%)	16% (±16%)	<0.001
Wide	24 (11%)	14% (±14%)	<0.001
Height	11 (5%)	15% (±17%)	0.05
Right	25 (11%)	23% (±19%)	<0.001
Left	17 (8%)	11% (±9%)	<0.01

Table 1. Distribution of the echocardiographic CoreValve stent frame shape and VARC-2 scores in all 223 patients. Data are displayed as number (percentage) and mean values (±SD).

Relation between Agatston score and stent frame eccentricity

The mean Agatston score was 3345± 1870. As seen in Table 2, the values according to the shapes were for circular stents: 2919± 1505 with 3241± 1774 in true circular stents and 2776 ± 1357 in near circular ones. The values for eccentric stents were 4159 ± 2116; W shape: 4139 ± 2320, H shape: 4757± 2639, R shape: 4299± 2076, and L shape: 3500± 1870. The correlation between the Agatston score and the amount of eccentricity, calculated as the post-TAVI echocardiographic stent eccentricity index, was significant (q=0.241, P=0.003).

Shape category	Patients	Agatston score	VARC-2 score	Pre-TAVI CT eccentricity index	Post-TAVI echo eccentricity index
Circular	106 (65%)	2919 ± 1505	4% (±7%)	21% (± 6%)	4% (±2%)
True circular	33 (20%)	3241 ± 1774	1% (±5%)	20% (± 7%)	0% (by definition)
Near circular	73 (45%)	2776 ± 1357	5% (±8%)	21% (± 6%)	6% (±2%)
Non-circular	56 (35%)	4159 ± 2116*	16% (±16%)*	21% (± 6%)	17% (±6%)*
Wide	20 (12%)	4139 ± 2320*	14% (±14%)*	19% (± 7%)	17% (±5%)*
Height	9 (6%)	4757 ± 2639*	15% (±17%)*	19% (± 7%)	15% (±6%)*
Right	16 (10%)	4299 ± 2076*	23% (±19%)*	22% (± 5%)	18% (±6%)*
Left	11 (7%)	3500 ± 1.870*	11% (±9%)*	20% (± 7%)	15% (±6%)*

Table 2. Distribution of the CoreValve stent frame shape, Agatston score, and VARC-2 score in the 162 patients with both pre-TAVI CT scan and pre-discharge echocardiography. *P < 0.05 compared to the Circular group.

Relation between native aortic annulus eccentricity and subsequent stent frame eccentricity

As seen in Table 2, the CT-derived eccentricity index of the native aortic annulus was not different between the circular, near-circular, and eccentric shaped stent frames as seen at pre-discharge echocardiography, nor was there a difference between the different shape types. Also, the correlation between the CT-derived eccentricity index of the native aortic annulus and the echocardiographic eccentricity index of the implanted stent was extremely poor (q=–0.016, P= 0.845).

Paravalvular leakage

The median PVL extent along the stent circumference as suggested by VARC-2 score was 3% (0–11%). Paravalvular leakage was absent in 91 cases (41%),mild in 67 (30%), moderate in 51 (23%), and severe in 14 (6%) cases. The correlation between stent frame eccentricity and PVL severity (VARC-2 score) was significant (q = 0.525, P <0.0001). As seen in Table 1, PVL was more often seen in non-circular stents than circular stents; the median VARC-2 value for circular was 0% (0–4%), while it was 12% (6–18%) for eccentric shapes (P <0.001). No significant differences in PVL extent were seen between particular stent frame shapes.

Relationship between stent eccentricity and location of paravalvular leakage

Distribution of sectors positive for PVL for each stent shape is reported in Figure 3. The number of patients with evidence of PVL in the area of the defined native commissures is displayed in Table 3, according to the commissure localization previously defined in Figure 1. Compared to (near) circular stent frames PVL occurred more often at the RLC in W, R, and L-shaped stent frames (63%, 68%, and 65% vs. 26%, respectively; all P < 0.05), at the LNC in W and R-shaped stent frames (50% and 64% vs. 16%; all P < 0.05), and at the RNC in the R-shaped stent frame only (28% vs. 7%; P< 0.05). Figure 4 shows the PVL localization in two patients with W and R-shaped stent frames, respectively.

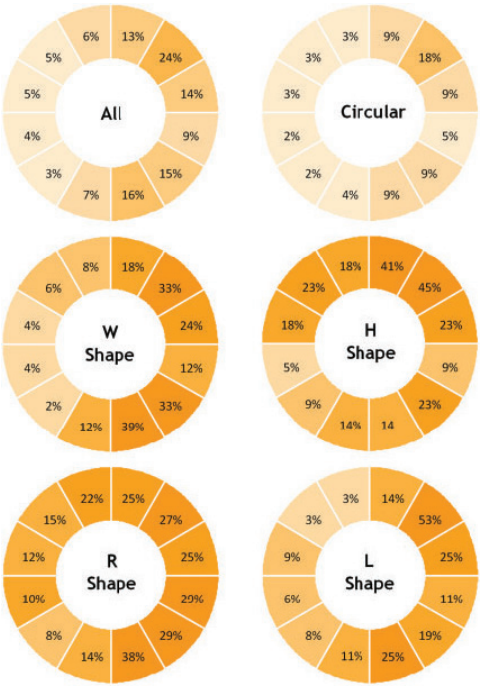

Figure 3. PVL distribution (percentage of patients with PVL seen in that specific hour) according to the clock model for the different stent frame shapes.

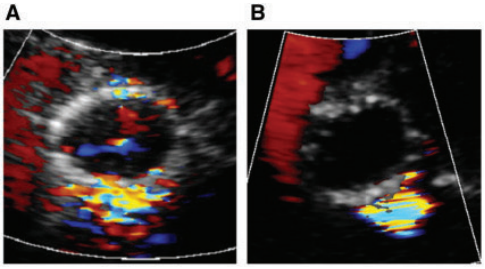

Figure 4. PVL localization in two patients with-Wand R shape, respectively. The W-shaped stent frame shows typically PVL in the upper and lower parts of the clock model and the R-shaped stent frame most typically shows PVL at the native commissure between the left and non-coronary cusps.

	Shape category				
	Circular	**W**	**H**	**R**	**L**
Right-left commissure (1–3 h)	38/146 (26%)	15/24 (63%)*	5/11 (45%)	17/25 (68%)*	11/17 (65%)*
Left-non commissure (5–7 h)	24/146 (16%)	12/24 (50%)*	5/11 (45%)	16/25 (64%)*	8/17 (47%)
Right-non commissure (9–11 h)	10/146 (7%)	3/24 (13%)	1/11 (9%)	7/25 (28%)*	3/17 (18%)
Any commisure	62/146 (42%)	21/24 (88%)*	9/11 (82%)*	25/25 (100%)*	15/17 (88%)*

Table 3. Site of aortic leakage in the different stent frame shapes in all 223 patients. *P < 0.05 compared to the Circular group. Aortic leakage included all severity categories.

Relationship between the CT-derived angle of the aortic annulus plane and stent eccentricity or paravalvular leakage

No significant correlations were found between the CT-derived angle of the aortic annulus and stent frame eccentricity. Also, no significant correlations were found with PVL severity or PVL location.

DISCUSSION

The main findings of this study are (1) approximately one third of CoreValve stent frames show a clear asymmetric shape at predischarge echocardiography, (2) the pre-TAVI Agatston score correlates–in contrast to the eccentricity index of the native aortic annulus–to the extent of frame eccentricity, (3) PVL severity correlates to the eccentricity of the stent frame, and (4) the site of PVL was dependent on the shape of the stent frame.

The relationship between the amount of calcification of the native aortic annulus measured as the aortic root Agatston score and the degree of PVL after TAVI has been described before in multiple studies (3,12-18) although in most of them PVL was not scored according to the current VARC-2 recommendations (8). In one study, the relation between the localization of calcium in the aortic annulus and the localization of PVL was also highlighted (13). However, the association between calcium score, stent frame eccentricity and subsequent PVL is not described in detail before.

For balloon-expandable devices it has been shown that consistent radial forces during the placement are developed, leading to a change in the structure of the aortic annulus which becomes less elliptic after the TAVI procedure (6,19,20). The CoreValve system instead only relies on the passive expansion of the nitinol structure to adhere to the aortic walls, and could be less effective in remodeling a calcified native valve, although it should be recognized that pre-dilatation in severely calcified aortic valves is often done. To our knowledge, no study has been published yet about the evaluation of the stent frame shape after the placement of a CoreValve prosthesis and the relation with PVL. One third of CoreValve stent frames showed an asymmetric shape at pre-discharge transthoracic echocardiography. Importantly, there was no relation between the native annulus shape and the eccentricity of the stent frame, so even in the self-expandable CoreValve device the native shapes seems to adapt to the prosthesis, rather than vice versa. On the other hand, the Agatston score correlated to the extent of stent frame eccentricity, so it is the calcium that defines the shape of the CoreValve prosthesis expansion. The eccentricity of the stent frame was strongly associated to the extent of PVL. According to the eccentricity, we defined several categories (profound irregularities other than these were only rarely seen). In order of prevalence these were the R-shape, W-shape, L-shape, and H-shape. Interestingly, the localization of the PVL was influenced by the shape

of the stent frame. Leakage at the RLC was more often seen in W, R, and L-shaped stent frames, leakage at the commissure between the LNC was more often involved in W, R-shaped stent frames, and leakage at the RNC was more often seen only in R-shaped stent frames. This is not surprising, as the particular configuration of the L-shaped stent frames is likely to be not well adherent to the aortic wall in the right upper quadrant, where the RLC is located. In contrast, the R-shaped stent frame is most likely to show PVL at the other commissures. Of note, the R-shaped stent frames also showed, as compared to circular stents, more PVL in the RLC but the increase was only 2.5-fold compared to 4-fold increases in PVL at the other two commissures. Finally, the W-shaped stent frame is most likely to be not well adherent to the wall at the LNC commissure sectors in the inferior sectors.

Clinical implications

The randomized CHOICE trial demonstrated more PVL with the self-expanding CoreValve than with the balloon expandable SAPIEN XT prosthesis (21). In addition, devices with a sealing fabric may perform better in patients with more annular calcification. The mechanically expanded Lotus valve has repeatedly demonstrated extremely favourable moderate PVL rates. Therefore, balloon-expandable transcatheter heart valves with more radial power may be preferred over mechanically expanded valves in cases of heavy annular calcification. However, a definite recommendation should be based on direct comparison between different devices in a randomized fashion with a pre-specified analysis for calcium burden.

Limitations of the present study

The data about the stent frame eccentricity and shape could be affected by the limitations of two-dimensional echocardiography since this technique is easily influenced by an incorrect scan plane or by suboptimal image quality. In this respect, it should be acknowledged that three-dimensional echocardiography and in particular transoesophageal echocardiography would be a superior technique (7). However, this was at the time not considered feasible in patients as a routine screening technique for PVL. In particular, a scanning plan not perfectly perpendicular to a circular stent could give the illusion of a H-shaped stent frame, while it is unlikely to result in a false W, R, or L-shaped stent frame. This may also be the explanation why the H shaped stent frames (that actually more often looked a little bit fuzzy) had the lowest prevalence of PVL and were not related to specific PVL localizations. Remarkably, however, the H-shape stent frame only accounted for the least number of cases in the present study. Conversely, it is possible to inadvertently 'correct' a real W-shaped stent frame to circular by choosing an oblique scan plan during image acquisition. The two-dimensional transthoracic echocardiographic defined stent shape should in the future be validated against a superior standard such as three-dimensional transoesophageal echocardiography or post-TAVI CT images. It would also be interesting to correlate stent frame eccentricity to other outcome parameters.

The direct effects of post-dilatation on PVL could not be assessed because in this study only the pre-discharge echocardiograms were assessed. Final stent eccentricity in patients with and without postdilatation was similar (data no reported).

Unfortunately, the CT software used in this study was not able to study the relation between the precise

site of calcium and subsequent stent frame shape (and thus PVL) (13).

CONCLUSIONS

Calcification of the aortic annulus is associated with a subsequent eccentric shape of the CoreValve prosthesis. This eccentric shape results in more PVL, with the localization of PVL related to the shape of stent frame eccentricity.

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CHAPTER XVI

Importance of contrast aortography with Lotus transcatheter aortic valve replacement. A post hoc analysis from the RESPOND post-market study

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ABSTRACT

Objectives

The aim of this post hoc analysis from the RESPOND (Repositionable Lotus Valve System–Post-Market Evaluation of Real World Clinical Outcomes) post-market study was to assess the final implantation depth on the contrast aortogram after Lotus valve (Boston Scientific, Marlborough, Massachusetts) transcatheter aortic valve replacement (TAVR) and to correlate with permanent pacemaker implantation (PPI) and paravalvular leak (PVL).

Background

Contrast aortography allows for the assessment of implantation depth and PVL during and after TAVR. Previous reports suggested an association between final device position and rates of PPI and PVL.

Methods

The RESPOND study was a prospective, open-label, single-arm study in 41 centers evaluating outcomes after Lotus TAVR in routine clinical practice. Aortograms were collected at the Erasmus Medical Center and analyzed by researchers who were blinded to clinical outcomes. The primary analysis correlated implantation depth with PPI and PVL and required aortograms in a coaxial projection. The relation between implantation depth and need for PPI was assessed by multivariate logistic regression, adjusting for pre-defined confounders. A secondary analysis compared PVL analysis by contrast aortography with transthoracic echocardiography (TTE) performed by the independent core laboratory.

Results

A total of 724 angiographic studies were included in this analysis. Mean Lotus implantation depth was 6.67 ± 2.19 mm. The overall PPI rate was 35%. PPI rate was lower with shallow implants (<6.5 mm: 21%vs. $6.5 mm: 41%; $p < 0.001$). After adjustment for confounders, implantation depth independently predicted need for PPI (odds ratio per 1-mm increment in depth: 1.200; 95% confidence interval 1.091 to 1.319; $p = 0.002$). More than trivial PVL was present in 23% by contrast aortography and in 8% by TTE. Implantation depth was not correlated with PVL by contrast aortography or TTE ($p = 0.342$ and $p = 0.149$, respectively). PVL grading by contrast aortography and TTE was concordant in 77%.

Conclusions

In this post hoc analysis of the RESPOND study PPI was highly correlated with implantation depth, whereas PVL was not. Higher Lotus implantation may reduce need for PPI.

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is recommended for symptomatic severe aortic stenosis in patients at elevated surgical risk (1–7). Multiple transcatheter heart valve (THV) designs are commercially available (8). The Lotus valve (Boston Scientific, Marlborough, Massachusetts) is a mechanically expanding system and includes an adaptive seal. These features make it completely repositionable and retrievable for precise placement as well as minimizing paravalvular leak (PVL) (9,10). The RESPOND (Repositionable Lotus Valve System–Post-Market Evaluation of Real World Clinical Outcomes) study was a prospective post-market study including 1,014 patients from 41 centers and confirmed Lotus valve safety and efficacy with an 2.6% all-cause mortality and 2.2% disabling stroke rate at 30 days with more than mild PVL in 0.3% and permanent pacemaker implantation (PPI) undertaken in 30% of patients (11). TAVR in its current form no longer requires general anesthesia and relies mostly on fluoroscopic guidance. Operators use contrast aortography to determine the implantation depth, device position relative to the coronary ostia, and final PVL assessment. The aim of this post hoc analysis from the RESPOND study was to assess the final implantation depth on the contrast aortogram after Lotus TAVR and to correlate with need for PPI and PVL.

METHODS

Study population and design

The design and outcomes of the RESPOND post-market study (NCT02031302) have been reported elsewhere (11). In brief, 1,014 patients with elevated operative risk were treated with Lotus TAVR and prospectively enrolled. An independent core laboratory (Cardialysis, Rotterdam, the Netherlands) analyzed the transthoracic echocardiography (TTE).

Clinical events were reported through electronic clinical research forms using the latest Valve Academic Research Consortium-2 criteria (12); all events were monitored by a contract research organization, and an external independent medical reviewer adjudicated death and stroke. The final contrast aortograms after implantation of the Lotus valve were collected and transferred to the Erasmus Medical Center for centralized uniform and blinded analysis. All patients provided written informed consent for participation in the RESPOND study. The primary objective of this study was to correlate depth of Lotus implantation with need for PPI and occurrence of more-than-trivial PVL by contrast aortography. A secondary analysis looked at the concordance of PVL grading between contrast aortography and pre-discharge TTE as assessed by the independent core laboratory.

Data quality

The current analysis used the as-treated population from the RESPOND study (n = 996) and excluded 132 patients with a pacemaker before TAVR. Of the 864 patients without a pacemaker a final contrast aortogram was not acquired in 140 patients, thus 724 cases were available for the final analysis.

For the PVL analysis contrast aortograms were submitted to the following quality check: 1) presence of sufficient contrast volume; 2) pigtail located >2 cm above the aortic annulus; and 3) no wire across the

Lotus valve. Of the 724 cases, 36 (5%) did not meet these criteria and were thus removed from the PVL analysis (Figure 1).

Previous reports suggested an error in measuring the implantation depth if the aortogram had been obtained in a noncoaxial projection (13). To address this matter, all participating centers were requested to perform a baseline and final aortogram in the same coaxial C-arm projection with the 3 coronary cusps aligned. Ultimately, 506 of 724 (70%) aortograms were acquired using a coaxial projection. Only aortograms in coaxial projection were used for the primary implantation depth analysis.

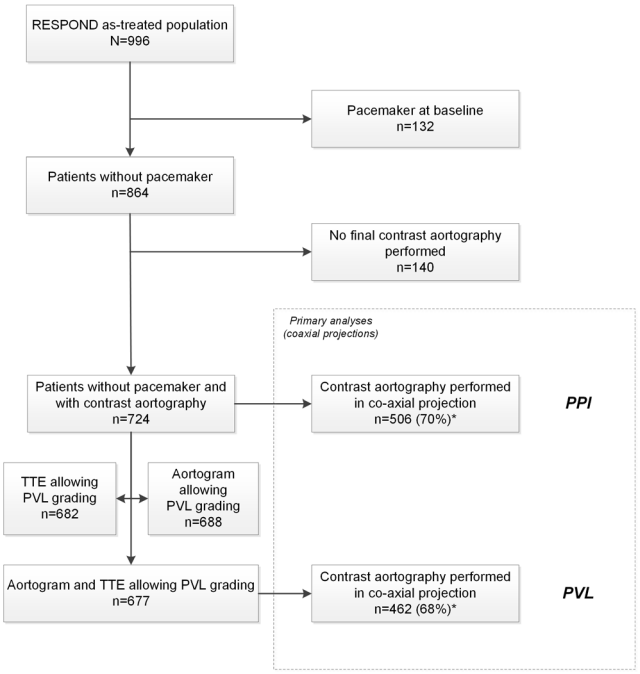


Figure 1. Flowchart of data collection. * aortograms that were acquired in a coaxial projection were used for the primary analysis. Abbreviations: PPI = permanent pacemaker implantation; PVL = paravalvular leak; RESPOND = Repositionable Lotus Valve System – Post-Market Evaluation of Real World Clinical Outcomes; TTE = transthoracic echocardiography.

Data analysis

Dedicated trained clinical researchers, who were blinded to clinical and echocardiographic results, analyzed all aortograms. Measurements were performed with Cardiovascular Angiographic Analysis System version 5.11.2 (Pie Medical Imaging, Maastricht, the Netherlands). Core measurements consisted of the final implantation depth at the noncoronary and left coronary cusps. The final implantation depth was considered as the average of the depth at the noncoronary cusp and left coronary cusp. Interobserver variability was evaluated using intraclass correlation coefficients in 10 randomly chosen subjects. Depth differential of the Lotus valve was measured as the difference in implantation depth at the noncoronary cusp and left coronary cusp. The degree of PVL was evaluated using the Sellers criteria (14) as follows: grade 1 (mild PVL), a limited amount of contrast enters the left ventricle during diastole resolving with each beat without reaching the apex of the left ventricle; grade 2 (moderate PVL), the contrast enters and fills the entire left ventricle up to the apex but the opacification remains less than in the ascending aorta; grade 3 (moderately severe PVL), complete left ventricular opacification with similar contrast density compared with the ascending aorta; and grade 4 (severe PVL), opacification of the entire left ventricle at a higher density than the ascending aorta. All TTE data were obtained from the independent core laboratory. PVL grading by TTE was according to Valve Academic Research Consortium-2 criteria (12).

Statistical analysis

Continuous data are presented as mean ± SD and categorical variables as counts and percentages. Categorical data were compared with the chi-square test for trend and Z-test for proportions. Due to

missing site-reported left ventricular outflow tract (LVOT) dimensions by computed tomography and the derived oversizing relative to the LVOT (38% missing), multiple imputation was performed for completion of this single variable, assuming this variable was missing at random (15). Five imputation steps were performed, using the following predictor variables: age, sex, weight, height, history of heart failure, history of coronary artery disease, atrial fibrillation, EuroSCORE (European System for Cardiac Operative Risk Evaluation), pre-existent conduction disturbances, annulus diameter (area derived), pre-dilatation, repositioning, valve prosthesis size, implantation depth, and need for PPI. Logistic regression was applied to evaluate the association between implantation depth and PPI using a predefined multivariate model with inclusion of the following clinically suspected confounders: age, sex, body mass index, coronary artery disease, pre-existent conduction disturbances (i.e., first-degree atrioventricular block, right bundle branch block RBBB, left bundle branch block, left anterior fascicular block), repositioning, pre-dilatation, high enrolling centers (>50 patients enrolled), oversizing relative to the LVOT, and depth differential of the prosthesis. The p values from multivariate analysis were adjusted for multiple comparisons using the Bonferroni correction. When p values exceeded 1.0 after Bonferroni correction the p value was truncated at 1.0. Data analysis was performed in SPSS version 21 (SPSS Inc., Chicago, Illinois). A 2-sided p value of <0.05 was considered statistically significant.

RESULTS

A total of 724 patients within the RESPOND study were eligible for this post hoc analysis (Figure 1). Baseline demographics are listed in Table 1. Mean age was 81 ± 7 years and 46% were men. Mean Society of Thoracic Surgeons Predicted Risk of Mortality Score was 6.1±

7.0%. Coronary artery disease was present in 54% of patients. A total of 36% had a history of congestive heart failure. Pre-existent conduction disturbances were present as follows: first-degree atrioventricular block in 13%, left bundle branch block in 9%, RBBB in 6%, and left anterior fascicular block in 4%. Procedural characteristics are listed in Table 2. The 3 available Lotus valve sizes were equally distributed among patients: 23 mm in 28% of patients, 25 mm in 40%, and 27 mm in 32%. Balloon pre-dilatation was performed in more than one-half of the patients (54%). Repositioning was attempted in one-third (32%).

Age, yrs	81 ± 7
Male	335 (46.0)
Body mass index, kg/m2	27 ± 8
Diabetes	201 (28.0)
Atrial fibrillation	217 (30.0)
Chronic obstructive pulmonary disease	109 (15.0)
Myocardial infarction	107 (15.0)
Coronary artery disease	391 (54.0)
Coronary artery bypass grafting	83 (11.0)
Percutaneous coronary intervention	213 (30)
Cerebrovascular accident	63 (9.0)
STS-PROM, %	6.1 ± 7
Porcelain aorta or hostile chest	42 (6.0)
Aortic valve area, cm2	0.74 ± 0.36
Mean aortic gradient, mm Hg	44 ± 18
First-degree atrioventricular block	93 (13.0)
Left bundle branch block	67 (9.0)
Right bundle branch block	44 (6.0)
Left anterior fascicular block	29 (4.0)
Left posterior fascicular block	3 (0.4)

Table 1. Baseline Characteristics (N = 724). Values are mean SD and n (%). Abbreviations: STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

Clinical outcomes

All-cause death at 30 days occurred in 12 (1.7%) patients, which were all due to cardiovascular causes. At 30 days, clinical stroke had occurred in 20 (2.8%) patients, of which 14 (1.9%) were disabling strokes. PPI AND PVL. PPI was required in 254 (35%) patients. The primary causes for PPI were high-degree atrioventricular block (67%) and bradycardia (9%). In 23% of patients PPI was performed for other reasons (e.g., bifascicular block, second-degree atrioventricular block Mobitz I type). By contrast aortography, more than trivial PVL was present in 164 (23%) patients: no PVL in 554 (77.2%) patients, mild PVL in 149 (20.8%) patients, moderate PVL in 14 (1.9%) patients, and moderate-to-severe PVL in 1 (0.1%) patient. By TTE, more than trivial PVL was present in 54 (7.9%) patients: none or trace in 628 (92.1%) patients, mild in 53 (7.8%) patients, and moderate in 1 (0.1%) patient.

Valve size	
23 mm	202 (28)
25 mm	289 (40)
27 mm	233 (32)
Pre-dilatation	387 (54)
Post-dilatation	9 (1)
Repositioning	231 (32)
Oversizing relative to the LVOT, %	
Overall	7 ± 8
23 mm	7 ± 8
25 mm	8 ± 7
27 mm	7 ± 8
Depth differential, mm*	-1.24 ± 3.05
Depth differential	
None (<2 mm)	358 (49)
Prosthesis at NCC >2 mm lower	281 (39)
Prosthesis at LCC >2 mm lower	85 (12)

Table 2. Procedural characteristics (N=724). Values are n (%) or mean SD. *Depth differential depicts the difference between implantation depth at the noncoronary cusp and left coronary cusp. Abbreviations: LVOT = left ventricular outflow tract.

Implantation depth

The interobserver variability for measuring the implantation depth was small (intraclass correlation coefficient 0.964; 95% confidence interval (CI) 0.858 to 0.991). Final mean implantation depth below the aortic annulus (i.e., average of depth at the noncoronary and left coronary cusp) was 6.67 ± 2.19 mm. Implantation depth had a normal distribution (Figure 2).

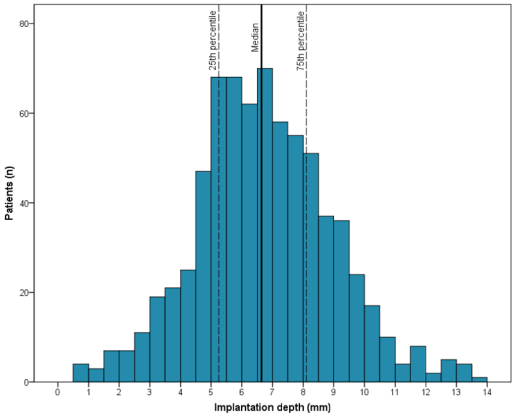


Figure 2. Histogram of implantation depth distribution over the entire cohort. The implantation depth (i.e., average of depth at the noncoronary and left coronary cusp) was normally distributed with a mean at 6.67 2.19 mm below the annulus.

Relation between implantation depth and PPI

PPI rates per implantation depth quartiles are listed in Table 3. There was a clear trend toward higher PPI rates with deeper implants ($p < 0.001$).

Implantation Depth Quartile				P-value for Trend
<5.0 mm (n = 104)	5.0–6.5 mm (n = 138)	6.5–8.0 mm (n = 127)	≥8.0 mm (n = 135)	
26 (25)	26 (19) *	46 (36) †	61 (45) †	<0.001

Table 3. PPI rates per implantation depth quartiles (coaxial projections only). Values are n (%). *No significant ifference compared to previous quartile at a 5% confidence level. †Significant difference compared to previous quartile at a 5% confidence level. Abbreviations: PPI = permanent pacemaker implantation.

Deeper implantation depth was associated with PPI by univariate analysis (odds ratio (OR) per 1-mm increment: 1.206; 95% CI 1.102 to 1.319; p < 0.001) in the primary analysis (Figure 3). When patients with non-coaxial projections were also included the implantation depth was still associated with an increased risk of PPI (OR: 1.172; 95% CI 1.091 to 1.258; p < 0.001) (Supplemental Figure 1).

After adjustment for predefined potential confounders, deeper implantation remained an independent predictor for PPI requirement (OR per 1-mm increment: 1.200; 95% CI 1.091 to 1.319; adjusted p = 0.002) (Figure 4). Additionally, repositioning also independently predicted PPI (OR: 1.927; 95% CI 1.261 to 2.945; adjusted p = 0.028). When patients with noncoaxial projections were also included both implantation depth (OR: 1.157; 95% CI 1.074 to 1.247; p = 0.004) and pre-existent RBBB (OR: 3.283; 95% CI 1.654 to 6.518; p = 0.014) independently predicted PPI (Supplemental Figure 2).

Mean oversizing was 7 ± 8% and did not differ between valve sizes (Table 2). Oversizing relative to the LVOT had no impact on PPI (p for trend = 0.195) (Supplemental Table 1).

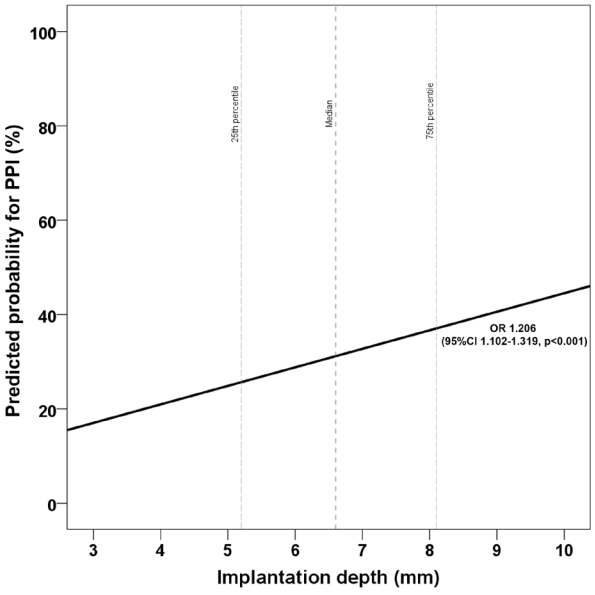
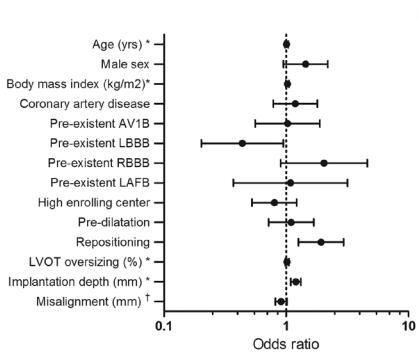


Figure 3. Relation Between Implantation Depth and PPI by Univariate Logistic Regression (Limited to Patients in Which Contrast Aortography Was Performed in a Coaxial Projection). The gray dashed lines indicate the median and interquartile range of implantation depth in the overall cohort. Abbreviations: CI = confidence interval; PPI = permanent pacemaker implantation; OR = odds ratio.



	Odds ratio	95% confidence interval	P-value	Adjusted P-value
Age (yrs) *	1.006	[0.975 - 1.037]	0.729	1.000
Male sex	1.440	[0.949 - 2.186]	0.086	1.000
Body mass index (kg/m2)*	1.023	[0.996 - 1.055]	0.131	1.000
Coronary artery disease	1.185	[0.783 - 1.793]	0.422	1.000
Pre-existent AV1B	1.024	[0.557 - 1.882]	0.940	1.000
Pre-existent LBBB	0.437	[0.202 - 0.945]	0.036	0.504
Pre-existent RBBB	2.037	[0.901 - 4.608]	0.088	1.000
Pre-existent LAFB	1.084	[0.369 - 3.182]	0.883	1.000
High enrolling center	0.800	[0.525 - 1.220]	0.300	1.000
Pre-dilatation	1.096	[0.716 - 1.678]	0.673	1.000
Repositioning	1.927	[1.261 - 2.945]	0.002	0.028
LVOT oversizing (%) *	1.014	[0.978 - 1.050]	0.440	1.000
Implantation depth (mm) *	1.200	[1.091 - 1.319]	<0.001	0.002
Misalignment (mm) †	0.908	[0.817 - 1.010]	0.076	1.000

Figure 4. Forest plot of logistic regression analysis for the primary endpoint, PPI (limited to patients in chich contrast aortography was performed in a coaxial projection). Only repositioning and implantation depth were significant predictors for permanent pacemaker implantation (PPI) in this model. The p values were adjusted for multiple comparisons using the Bonferroni correction. *Odds ratios illustrate the increase in odds per 1-point increase on a continuous scale. †Depth differential depicts the difference between implantation depth at the noncoronary cusp and left coronary cusp. Abbreviations: AV1B = first-degree atrioventricular block; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LVOT = left ventricular outflow tract; RBBB = right bundle branch block.

Relation between implantation depth and PVL

There was no correlation between implantation depth and presence of more than trivial PVL by TTE (p for trend = 0.149) or contrast aortography (p for trend = 0.342) (Figure 5).

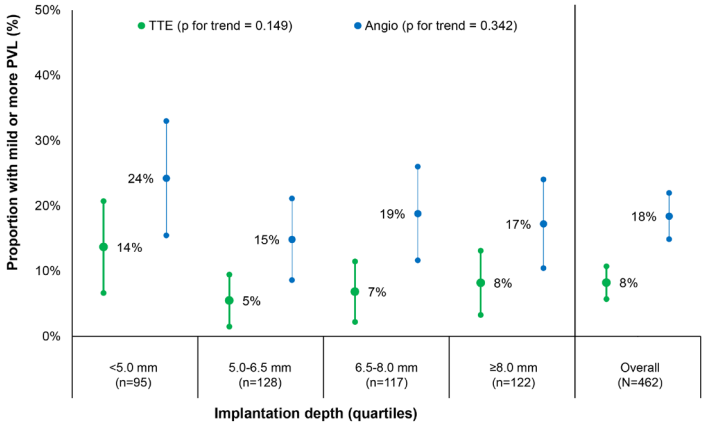


Figure 5. PVL (more than trivial) per implantation depth quartile (limited to patients in which contrast aortography was performed in a coaxial projection). Implantation depth was not related to PVL on TTE or aortogram.

Concordance of PVL grading between imaging strategies

PVL grading by contrast aortography and TTE were concordant in 77% of patients (Figure 6). A total of 19% of patients had more-than-trivial PVL by contrast aortography but not by TTE at discharge. Conversely, 4% of patients had more than trivial PVL by TTE at discharge and not by contrast aortography. In all patients with moderate PVL by contrast aortography (n = 14) the PVL was either mild (n = 7) or none/trace (n = 7) by TTE. One patient had moderate-to-severe PVL by contrast aortography and died during the index procedure without echocardiographic analysis. Moderate PVL by TTE was present in 1 patient. Interestingly, this patient had no visible PVL by aortography.

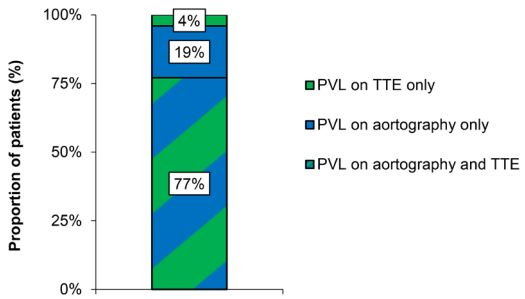


Figure 6. Concordance of more-than-trivial PVL between contrast aortography and TTE. In the vast majority of patients (77%) PVL as detected on aortography was also present on TTE. In a considerable proportion of patients (19%) PVL was detected on aortography, but not on TTE. The reverse occurred seldom (4%).

DISCUSSION

This post hoc analysis from the RESPOND study reports advanced insights from contrast aortography after Lotus TAVR. First, meticulous contrast aortography technique following Lotus TAVR is a prerequisite for adequate evaluation of PVL and Lotus depth of implantation. Second, deeper Lotus implants lead to more frequent PPI. Third, contrast aortography allows for a proper PVL assessment and seems more sensitive than TTE. Interestingly, all patients with more than mild PVL by contrast aortography (Sellers grade ≥2) had either no or trivial or mild PVL by TTE. Contrast aortography thus offers important insights for Lotus TAVR guidance, including prediction of PPI and acceptable PVL evaluation in conscious patients.

TAVR is increasingly executed under local anesthesia with or without conscious sedation with favourable results (16,17). The obvious advantages of local anesthesia include patient comfort, hemodynamic stability, rapid detection of complications (stroke, vascular complications), faster recovery, and shorter intensive care and hospital stay (18). Transesophageal echocardiographic guidance is challenging with TAVR under local anesthesia. Therefore, valve positioning and evaluation of PVL predominantly relies on fluoroscopic guidance and contrast aortography.

Pre-procedural planning by 3-dimensional multi-slice computed tomography scanning and new TAVR designs improved transcatheter valve sizing and positioning (8) with excellent clinical outcome and low PVL rates (11,19,20). Two randomized trials have established TAVR feasibility in patients at intermediate operative risk (5,6), and challenging anatomies (21). However, high PPI rates remain a matter of concern with new generation devices: ≈13% with the SAPIEN 3 (Edwards Lifesciences, Irvine, California) (20), ≈17% with the Evolut R (Medtronic, Minneapolis, Minnesota) (19), and 30% with the Lotus (10,11).

Conduction disorders following TAVR may occur because of the close proximity of the atrioventricular node, bundle of His, and left bundle branch to the native aortic annulus (22,23). It seems plausible that deeper implants of a THV result in more interaction with the conduction system that could lead to more PPI.

Several studies reported a correlation between CoreValve (Medtronic) implantation depth and PPI (24–26). Also with balloon-expandable THVs there seems to be a relation between implantation depth and persistent conduction disturbances or PPI (27–29). Currently, aiming for higher implants is recommended in order to reduce the need for PPI.

A subanalysis from the randomized REPRISE-II (Repositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus Valve System II) study demonstrated only a weak (nonsignificant) correlation between implantation depth and need for PPI with the repositionable Lotus valve (30). The fact that the present post hoc analysis from the RESPOND study did demonstrate a strong correlation is most plausibly due to the methodological setup of the study. It represents the largest study to date with systematic measurements of implantation depth and outnumbers the REPRISE-II study or any other study with different devices for that matter. Furthermore, by dichotomizing the implantation depth (i.e., ≤5 mm vs. >5 mm), the REPRISE-II study consequently lost statistical power to demonstrate the correlation with PPI (30). The present study reveals a linear relation between Lotus implantation depth and PPI requirement after correction for multiple confounders. The mean implantation depth of 6.67 mm leaves room for improvement by device alterations on the one hand and operator awareness on the other hand. Depth Guard (Boston Scientific, Marlborough, Massachusetts) is a recent alteration that may improve accuracy in Lotus positioning enabling higher implants (Figure 7). Ongoing studies will determine whether PPI rates will fall with Depth Guard.

In this study, repositioning predicted PPI as well. Lotus radial strength and interactions at multiple different locations within the LVOT during repositioning may promote conduction disorders.

With the self-expanding CoreValve, PVL was associated with too high or too low implants (31–34). In the REPRISE-II trial, high Lotus implants were associated with mild or moderate PVL (35). In contrast, our study suggests high Lotus implants are not associated with PVL. The adaptive seal of the outer skirt

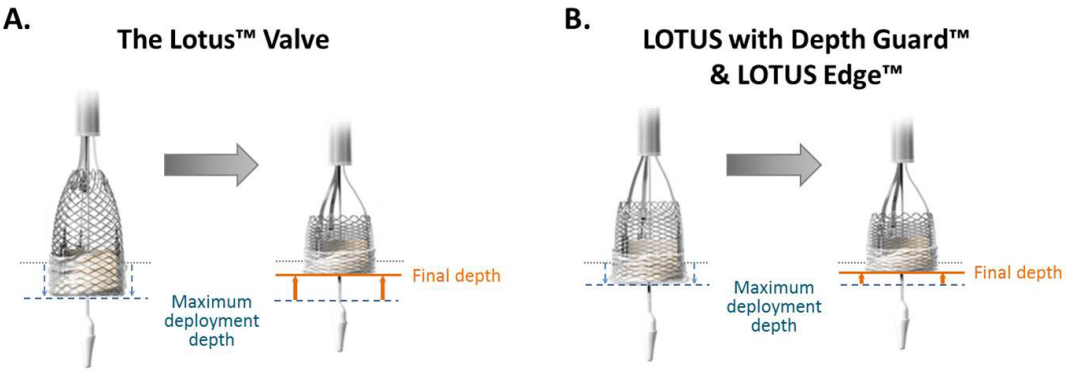


Figure 7. Lotus Depth Guard technology. (A) The current-generation Lotus valve (Boston Scientific, Marlborough, Massachusetts) results in deep left ventricular outflow tract (LVOT) interaction due to the foreshortening from both ends that occurs during locking of the valve. (B) The next-generation Lotus valve with Depth Guard technology involves foreshortening of the stent frame from the top down during unsheathing. This results in a less deep protrusion of the distal edge of the stent frame into the LVOT. Consequently, LVOT protrusion with Depth Guard is predictable and less pronounced resulting in less interaction with the LVOT. Courtesy of Boston Scientific Inc.

seems to cover periprosthetic spaces and adequately prevents PVL. Also the latest balloon expandable and self-expanding THV have a sealing fabric to help reduce PVL (8).

Periprocedural PVL assessment is essential for TAVR success. Current trends of performing TAVR under local anesthesia and mild or no sedation make transesophageal echocardiography less suitable for PVL assessment. Many centers now rely more on contrast aortography, TTE, and hemodynamic assessment. The present study showed an overall 77% concordance between the per-procedural semi-quantitative Sellers grading by contrast aortography and core laboratory–evaluated pre-discharge TTE. Interestingly, contrast aortography seemed more sensitive to detect PVL because in 19% PVL was detected by aortography but not by pre-discharge TTE, though it is possible that this difference might be at least partially explained by improvement in PVL between the time of the aortogram and echocardiography. This signal for a higher sensitivity for PVL detection by immediate aortography as compared with pre-discharge TTE was also observed in the randomized CHOICE (Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis) trial (36). Both modalities, contrast aortography and TTE, have their inherent pitfalls in the detection of PVL (37). First, contrast aortography is performed during the procedure, whereas TTE is performed several days thereafter. In many centers TAVR still occurs under general anesthesia, which by itself affects hemodynamics. Also, PVL might dissolve over days due to continued frame expansion and settling of the sealing skirt.

Second, PVL grading by TTE may suffer from artifacts such as acoustic shadowing of the stented frame and merging jets from multiple directions. With contrast aortography, power injection too close to the bioprosthesis may induce PVL or overlapping anatomical entities such as the spine or the descending thoracic aorta may influence the interpretation of the aortogram (38,39). New software tools, such as video-densitometric aortography, may further improve the reliability and reproducibility of contrast aortography (39,40).

Study limitations

This subanalysis of the RESPOND post-market study represents the largest cohort to evaluate contrast aortography after TAVR. However, the following limitations should be acknowledged. Although data collection and validation was rigorous and the population size was large, the observational design of this post hoc analysis must be acknowledged. Therefore, our findings may require confirmation by further study.

Acquisition of a post-implantation aortogram is part of the default workflow of a Lotus TAVR. Nevertheless, in 1 of 6 patients this aortogram was not available for final analysis due to logistical reasons. Aortograms were executed by the local TAVR teams according to local standards. Aortogram quality and coaxiality affect device implantation depth analysis. Despite study recommendations 30% of the aortograms were obtained in a noncoaxial projection and 2% were of insufficient quality for accurate PVL grading. Also, the decision to proceed with PPI was per treating physician's discretion.

Even with more shallow implants PPI rate was relatively high after Lotus implantation and suggests improving the implantation depth would only partly solve the pacemaker issue with this device.

Finally, we compared procedural contrast aortography with pre-discharge TTE. PVL may have changed within this time window and this may have impacted the comparison between the 2 modalities. Contrast aortography suffers from inherent limitations such as challenging determination of PVL mechanism and location. Also, it requires potentially harmful administration of intravascular contrast, especially in case of repeated aortograms. Nevertheless, apart from aortic regurgitation assessment aortography is essential in contemporary TAVR practice to determine coronary patency and device position.

CONCLUSIONS

In this post hoc analysis of the RESPOND study PPI was highly correlated with Lotus implantation depth, whereas PVL was not. Higher Lotus implantation may reduce need for PPI.

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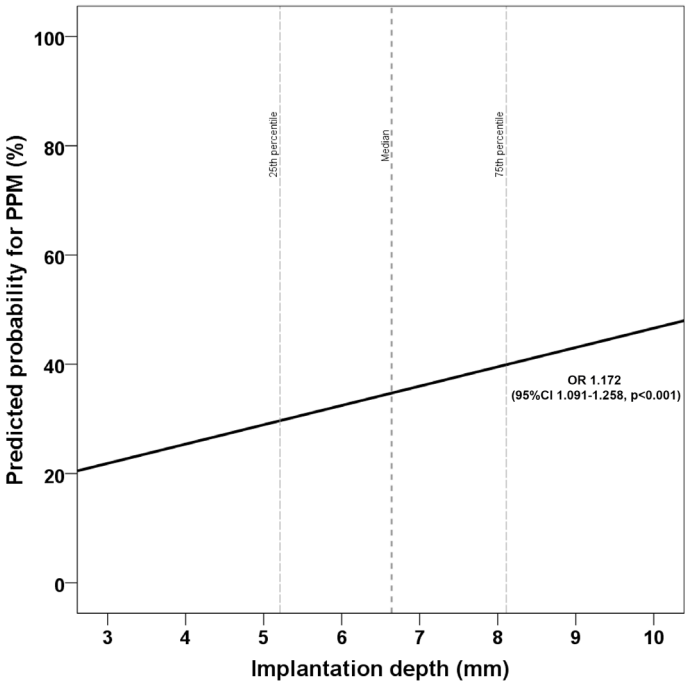
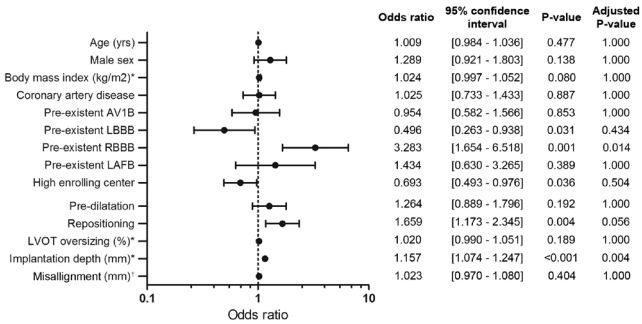
SUPPLEMENTAL MATERIAL



Supplemental figure 1. Relation between implantation depth and PPI by univariate logistic regression in the overall cohort. The grey dashed lines indicate the median and interquartile range of implantation depth in the overall cohort.



Supplemental figure 2. Forest plot of logistic regression analysis for the primary endpoint PPI in the overall cohort. Only pre-existent RBBB and implantation depth were significant predictors for PPI in this model. P-values were adjusted for multiple corrections using the Bonferroni correction. *Odds ratios illustrate the increase in odds per 1 point increase on a continuous scale. † depth differentiation depicts the difference between implantation depth at the noncoronary cusp and left coronary cusp. Abbreviations: AV1B: First degree atrioventricular block, LAFB: left anterior fascicular block, LBBB: left bundle branch block,LVOT: left ventricular outflow tract, RBBB: Right bundle branch block.

Oversizing % quartiles				P-value for trend
< 3% (n=85)	3-7% (n=86)	7-11% (n=85)	≥ 11% (n=87)	
23 (26%)	31 (36%)	34 (40%)	24 (28%)	0.195

Supplemental table 1. PPI rates per oversizing % quartiles (coaxial projections only). There was no trend towards higher PPI rates with more oversizing.

Part V
Future perspectives

CHAPTER XVII

Prognostic implications of moderate aortic stenosis in patients with left ventricular systolic dysfunction

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ABSTRACT

Background

Left ventricular (LV) systolic dysfunction and moderate aortic stenosis (AS) are more frequent with advancing age and often coexist. Afterload reduction is the mainstay of pharmacological treatment of heart failure (HF). Aortic valve replacement (AVR) is only formally indicated for symptomatic severe AS.

Objectives

This study sought to determine the clinical outcome of patients with concomitant moderate AS and LV systolic dysfunction.

Methods

Echocardiographic and clinical data of patients with moderate AS and LV systolic dysfunction between 2010 and 2015 from 4 large academic institutions were retrospectively analyzed. Moderate AS was defined as aortic valve area between 1.0 and 1.5 cm2 and LV systolic dysfunction defined as LV ejection fraction <50%. The primary endpoint was a composite of all-cause death, AVR, and HF hospitalization.

Results

A total of 305 patients (mean age 73 ± 11 years; 75% male) were included. The majority were symptomatic at the time of index echocardiogram (New York Heart Association (NYHA) functional class II: 42%; NYHA functional class III: 28%; and NYHA functional class IV: 4%). Ischemic heart disease was present in 72% of patients. At 4-year follow-up, the primary composite endpoint occurred in 61%. The main predictors for the primary endpoint were male sex ($p = 0.022$), NYHA functional class III or IV ($p < 0.001$), and peak aortic jet velocity ($p < 0.001$). The rate of the composite of all-cause death or HF hospitalization was 48%, rate of all-cause death was 36%, and rate of HF hospitalization was 27%. AVR occurred in 24% of patients.

Conclusions

Patients with concomitant moderate AS and LV systolic dysfunction are at high risk for clinical events. Further studies are needed to determine if earlier AVR in these patients might improve clinical outcome.

INTRODUCTION

Heart failure (HF) affects up to 15% of the elderly population older than age 70 years (1,2). These patients still face a grim prognosis, with 1- and 5-year mortality rates of approximately 20% and 50%, respectively (3,4). After hospital admission for HF, the 1-year rehospitalization or mortality rate is as high as 20% to 80% (5). Pharmacological management of HF includes beta-blockers and modulation of the renin-angiotensin-aldosterone system to reduce afterload (1,2). Degenerative aortic stenosis (AS) is a common valve disease affecting 2% to 4% of patients older than age 65 years (6,7); therefore, it often coexists with left ventricular (LV) systolic dysfunction. AS gradually progresses, with an annual reduction in aortic valve area (AVA) of ≈0.1 cm^2 (8,9), and may contribute to LV systolic dysfunction through afterload mismatch (10). Mortality with severe AS approximates 50% after 2 years of follow-up after symptoms occur or LV systolic dysfunction is present (11). Aortic valve replacement (AVR) is currently indicated for patients with symptomatic, severe AS (12,13), but not for moderate AS. Life expectancy in patients with moderate AS (8,14–18) may be reduced, especially in combination with coronary artery disease and LV systolic dysfunction (14). The aim of the present study was to evaluate the clinical outcome of patients with moderate AS and LV systolic dysfunction in terms of death, AVR, and hospital admissions for HF.

METHODS

The echocardiography databases from 4 academic centers in the United States, Canada, and the Netherlands, between January 2010 and December 2015, were screened for patientswithmoderate AS and LV systolic dysfunction. Moderate AS was defined as AVA >1.0 and <1.5 cm^2 and peak aortic jet velocity (Vmax) >2 and <4 m/s at rest or after dobutamine stress echocardiography (DSE). LV systolic dysfunction was defined by a left ventricular ejection fraction (LVEF) <50%. The AVA was calculated using the continuity equation, and LVEF was determined by the biplane Simpson's method (19,20). Patients with AVA <1 cm^2 suspected of having pseudo-severe AS were only eligible for this study when DSE revealed an AVA >1 cm^2. Exclusion criteria were prior major aortic surgery, prior surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR), hypertrophic or noncompaction cardiomyopathy, and congenital heart disease (i.e., unicuspid or bicuspid aortic valve disease determined unequivocally by transthoracic echocardiography). Patient demographics and clinical follow-up information were collected from hospital records or requested from treating physicians and referring centers. Survival status was obtained from the respective National Population Registries whenever possible. In the United States, survival status was determined through hospital records and obituaries. The study was carried out under the approval of the Erasmus Medical Center Institutional Review Board.

Study endpoints

The primary endpoint of the study was a composite of all-cause death, AVR (i.e., SAVR or TAVR), and HF hospitalization. If the patient was admitted for HF at the time of the index echocardiogram, the first event thereafter was considered an endpoint. Secondary endpoints included the composite of death and rehospitalization as well as each individual component of the primary composite endpoint.

Statistical analysis

Continuous data are presented as mean ± SD or confidence intervals (CIs) when applicable, or median and interquartile range (IQR) depending on distribution. Distribution of data was checked with histograms and the Shapiro-Wilk test. Categorical variables were compared with the chi-square test for trend. Continuous variables at different time points were compared using the paired Student t test. Cumulative incidence functions of the pre-defined composite endpoint—death, AVR, and HF hospitalization—were determined using the Kaplan-Meier method, with date of the index echocardiogram as initial time of follow-up (t = 0). Cumulative incidences were evaluated per year of follow-up to determine trends in timing of occurrence. Survival analyses for the primary endpoint were stratified for LVEF, New York Heart Association (NYHA) functional class, and HF admission. To determine the cumulative incidence function in patients admitted for HF, the admission date was computed as initial time of follow-up (t = 0). A log-rank test was applied to compare between-group differences. Univariate and multivariate Cox proportional hazard regression analyses were performed to identify independent predictors of the primary composite endpoint. Cox regression was performed in a 2-step hierarchical fashion to account for potential variation in outcome between institutions. A p value < 0.20 in the univariate model was used as an entry criterion for the multivariate model.

Individual components of the primary endpoint were analyzed using the cumulative incidence competing risk method, accounting for death and AVR as competing risks (21,22). Data analysis was performed using SPSS version 21 (IBM, Armonk, New York). A 2-sided, p value < 0.05 was considered statistically significant.

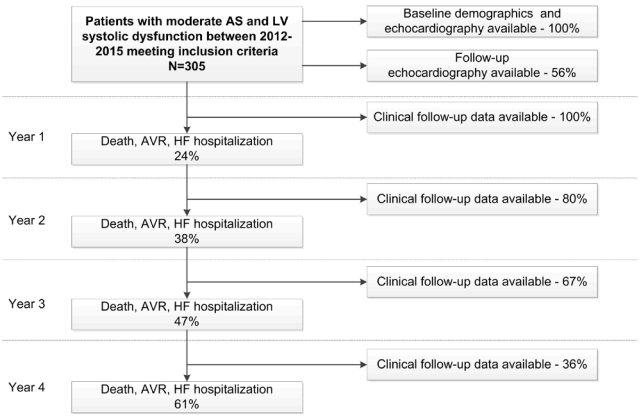

Figure 1. Study flowchart. In total, 305 patients were identified as having moderate aortic stenosis (AS) and left ventricular (LV) systolic dysfunction by pre-defined criteria. After 4 years of follow-up, 61% of patients reached the primary composite endpoint of all-cause death, aortic valve replacement (AVR), or heart failure (HF) hospitalization. Availability of clinical data decreased as the follow-up time increased due to loss to follow-up. A follow-up echocardiography had been obtained in 56% of the patients.

RESULTS

The study included 305 patients with baseline echocardiograms between January 2010 and December 2015. Baseline characteristics are listed in Table 1. The mean age was 73 ± 11 years, and 75% were male. The majority had coronary artery disease, with prior revascularization by percutaneous coronary intervention in 36% and coronary artery bypass grafting (CABG) in 28%. One-third (34%) had NYHA functional class III or IV symptoms at baseline. A total of 23 patients (7.5%) were admitted to the hospital at the time of the index echocardiogram. In terms of baseline therapy, nearly three-quarters were taking beta-blocking agents, and one-half angiotensin-converting enzyme inhibitors; fewer had angiotensin receptor blockers or mineralocorticoid receptor antagonists in their regimens (Table 2). Overall, 13% of patients received a regimen of beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and mineralocorticoid receptor antagonists. Cardiac resynchronization therapy was present in 13% of patients.

Index echocardiographic parameters are listed in Supplemental Table 1. The mean LVEF was 38 ± 9%; AVA 1.24 ± 0.16 cm²; indexed aortic valve area (AVAi) (AVA divided by body surface area (BSA)) 0.64 ± 0.12 cm²/m²; Vmax 2.5 ± 0.4 m/s; peak transaortic gradient 26 ± 8 mm Hg; and mean transaortic gradient 14 ± 4 mm Hg. The majority had a mean transaortic gradient <20 mm Hg (81%) or Vmax <3.0 m/s (84%). DSE was performed in 11% of patients to exclude severe AS and confirm moderate AS. Concerning AVAi, 56% of patients had an AVAi 0.6 to 0.9 cm²/m² versus 33% with AVAi <0.6 cm²/m². One-fifth of patients with

		N=305
Demographics		
Age (years)		73 ± 11
Male gender		229 (75%)
Diabetes		116 (38%)
Hypertension		225 (74%)
Dyslipidemia		217 (71%)
Coronary artery disease		219 (72%)
Prior myocardial infarction		159 (52%)
Prior PCI		109 (36%)
Prior CABG		86 (28%)
Chronic lung disease		75 (25%)
Revascularization		155 (51%)
Creatinin level (mmol/L)		109 ± 73
eGFR in (ml/min)		61 ± 20
Ischemic cardiomyopathy		140 (48%)
Smoking		63 (22%)
Peripheral arterial disease		60 (20%)
Prior stroke		43 (14%)
NYHA-class	I	79 (26%)
	II	129 (42%)
	III	86 (28%)
	IV	12 (4%)
Index-echocardiography		
LVEF (%))		38 ± 9
AVA (cm2)		1.24 ± 0.16
Vmax (m/s)		2.5 ± 0.4
PG (mmHg)		27 ± 9
MG (mmHg)		15 ± 5

Table 1. Baseline characteristics. Values are mean SD or n (%)). *Body mass index ≥30 kg/m2. Abbreviations: AVA = aortic valve area; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; Vmax = peak aortic jet velocity.

Cardiac resynchronization therapy	38 (13%)
Medication use	
Beta-blocker	216 (73%)
ACE-i	143 (48%)
ARB	83 (28%)
MRA	62 (21%)
Combined Beta-blocker (ACE-i/ARB and MRA	39 (13%)
Other diuretic	194 (65%)
Digoxin	19 (9%)
Nitrate	81 (38%)
Calcium antagonist	99 (34%)
Statin	223 (75%)
Acetylsalicylic Acid	196 (66%)
OAC	129 (43%)
P2Y12 receptor inhibitor	71 (24%)

Table 2. Therapy at time of index echocardiography. Values are n (%)). Abbreviations: ACE-i = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; MRA = mineralocorticoid receptor antagonist.

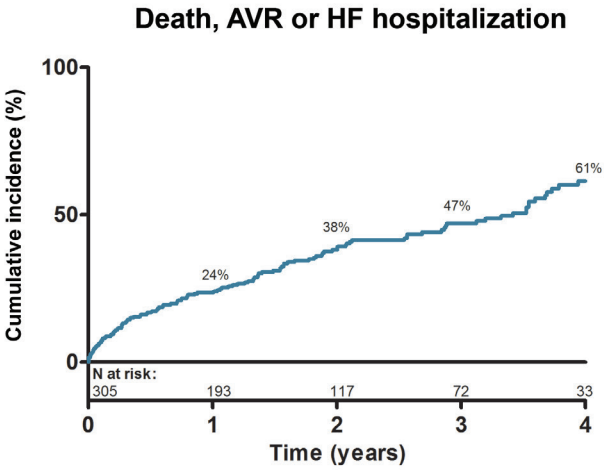

Figure 2. Incidence of the composite primary endpoint. Cumulative incidence increased to 61% at 4-year follow-up, with the steepest increase during the first year following the index echocardiogram. The findings implicated that this population faces a high clinical event rate.

AVAi 0.6 to 0.9 cm²/m² presented with a body mass index >30 kg/m² versus 50% of patients with AVAi <0.6 cm²/m².

Primary endpoint

Follow-up data were available for 80% of patients beyond 1 year after the index echocardiogram, for 67% beyond 2 years, and for 36% beyond 3 years (Figure 1). The median follow-up time was 638 days (IQR 280 to 1,137 days). At 4-year follow-up, the event rate for the primary composite endpoint was 61% (95% CI 54.38% to 67.78%) (Figure 2). The primary composite endpoint appeared to occur predominantly in the first year after the index echocardiogram compared with the years thereafter (Figure 3). The event rate was higher in patients with HF admission at time of the index echocardiogram compared with the overall cohort (log-rank p < 0.001) (Figure 4).

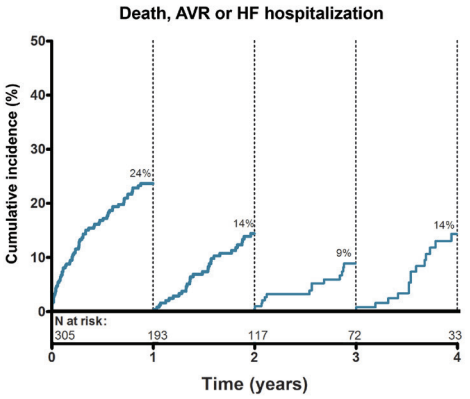

Figure 3. Primary composite endpoint at yearly intervals. According to the cumulative incidence curve per year of follow-up for all-cause death, AVR, or HF hospitalization, the event rate is highest in the first year after diagnosis.

The univariate analysis is presented in Supplemental Figure 1. Male sex (hazard ratio (HR): 1.75; 95% CI 1.16 to 2.64; p = 0.008), diabetes (HR: 1.51; 95% CI 1.09 to 2.10; p = 0.014); chronic lung disease (HR: 1.59; 95% CI 1.11 to 2.29; p = 0.012), NYHA functional class III or IV (HR: 2.86; 95% CI 1.70 to 4.24; p < 0.001), and Vmax (HR: 2.24 per 1 m/s increment; 95% CI 1.47 to 3.42; p < 0.001) emerged as main predictors for the composite primary endpoint by multivariate analysis (Figure 5). Patients with baseline NYHA functional class III or IV symptoms had a 4-year event rate of 84% (95% CI 76.92% to 89.21%), compared with 54% for NYHA functional class II (95% CI 41.65% to 64.81%; log-rank p < 0.001) and 45% for NYHA functional class I (95% CI 25.77% to 61.90%; log-rank p < 0.001) (Figure 6). There was no statistically significant difference in event rate for patients with an LVEF ≤35% compared with patients with an LVEF >35% (4-year follow-up: 71% vs. 55%; log-rank p = 0.092) (Supplemental Figure 2). When we divided the study population in tertiles based on AVAi, we could not detect any difference in event rate (log-rank p = 0.107) (Supplemental Figure 3). The event rates were similar among the 4 individual institutions (log-rank p = 0.515) (Supplemental Figure 4).

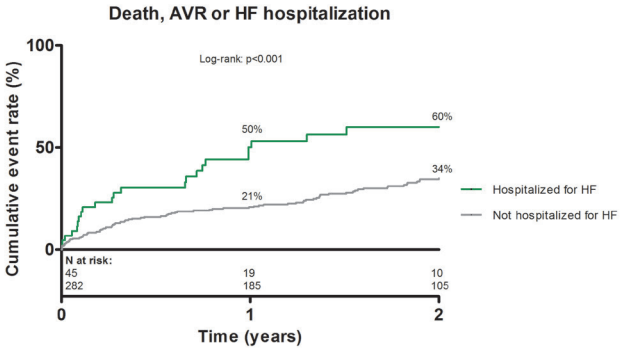

Figure 4. Composity primary endpoint stratified by HF hospitalization. During the first 2 years of follow-up, patients who were hospitalized at time of index echocardiogram appeared to be more prone to clinical events than those who were not hospitalized at that time. (For patients admitted for HF, date of admission is t = 0).

At 4-year follow-up, the rate of the composite of all-cause death or HF hospitalization was 48% (95% CI 40.65% to 56.61%) (Figure 7A), all-cause death was 36% (95% CI 28.68% to 44.80%) (Figure 7B), and cumulative HF hospitalization

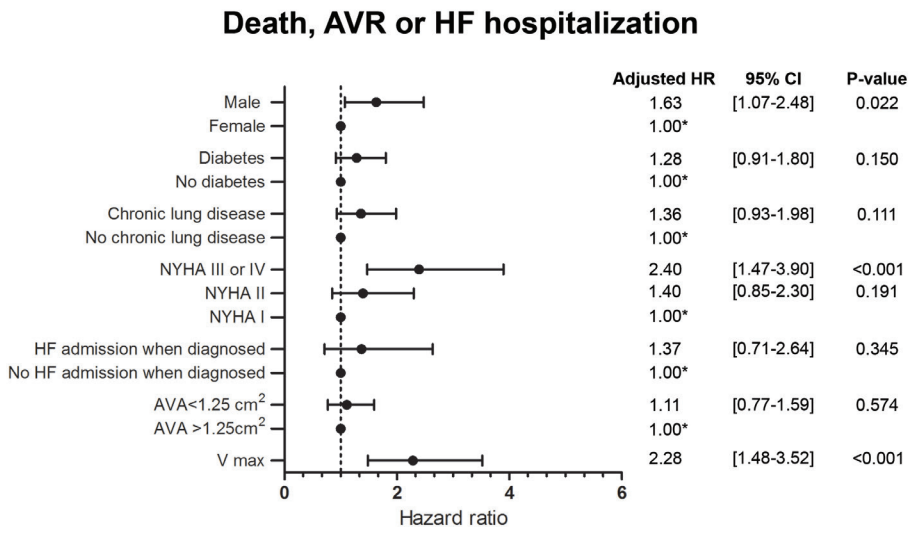

Figure 5. Multivariate cox regression analysis. A 2-step hierarchical multivariate Cox regression model was conducted to evaluate predictors for the primary composite endpoint; the purpose of the hierarchical structure was to account for variation between institutions. Variables were selected if they met the entry criterion in univariate regression. *Reference category.

rate was 27% (95% CI 20.32% to 35.67%) (Figure 7C). New hospital admissions for HF occurred in 43% of patients who were admitted for HF at time of index echocardiogram (n = 23) versus 4% in patients who were not admitted for HF at time of index echocardiogram (n = 282) (p < 0.001). The rate of AVR was 24% (95% CI 18.96% to 31.44%) (Figure 7D), including SAVR in 63% and TAVR in 37%. The majority of SAVRs did not involve simultaneous CABG (31 of 37; 84%). The median time to SAVR or TAVR was 133 days (IQR 22 to 543 days).

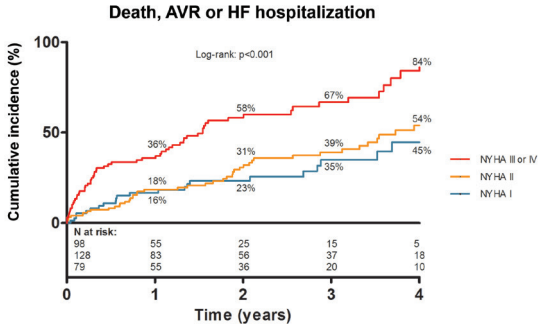

Figure 6. Composite primary endpoint stratified by NYHA functional class. Patients in NYHA functional class III or IV had a worse prognosis compared with patients in lower NYHA functional classes.

Echocardiography at follow-up

More than one-half of the patients (172 of 305; 56%) underwent a follow-up echocardiogram before the study end date. The median time between the index echocardiogram and follow-up echocardiogram was 541 days (IQR 337 to 890 days) and 467 days (IQR 315 to 937 days) for patients who were medically treated and underwent AVR, respectively. During follow-up, AVA decreased on average from 1.24 ± 0.16 cm² to 1.14 ± 0.25 cm² (p < 0.001) in patients who were medically treated and from 1.23 ± 0.14 cm² to 1.00 ± 0.22 cm² (p = 0.004) in patients who underwent subsequent AVR. The evolution of echocardiographic parameters is displayed in Supplemental Table 1.

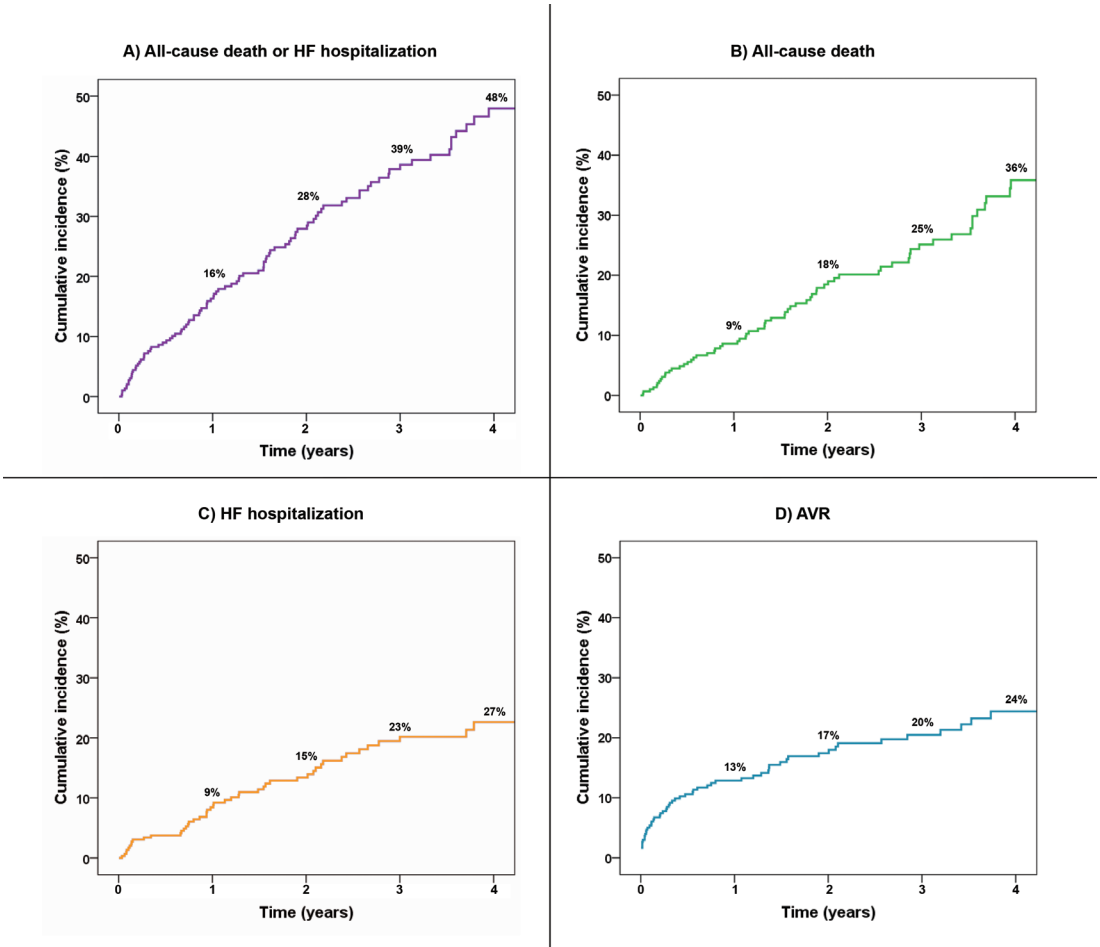

Figure 7. Competing risk curves for individual endpoints. A cumulative incidence competing risk analysis was conducted to evaluate the cumulative incidence of the individual components of the primary endpoint: (A) all-cause death and HF hospitalization; (B) all-cause death; (C) HF hospitalization; and (D) AVR. The individual endpoints were all common, confirming that the occurrence of clinical events in patients with moderate AS and LV systolic dysfunction is multifactorial.

DISCUSSION

This longitudinal multicenter cohort study reported the clinical outcome of consecutive patients with moderate AS and LV systolic dysfunction. The main findings can be summarized as follows: 1) the composite primary endpoint of all-cause death, AVR, or HF hospitalization occurred in 61% of patients at 4-year follow-up; 2) male sex, NYHA functional class III or IV, and higher transaortic Vmax on the index echocardiogram were independent predictors of events; 3) most events occurred during the first year after the diagnosis; and 4) patients admitted for HF at time of inclusion were particularly vulnerable and had event rates of 50% and 60% at 1 and 2 years, respectively (Figure 8).

The combination of moderate AS and LV systolic dysfunction in the general population is likely under-reported and is expected to grow with an aging population. A large population-based study concluded that the prevalence of moderate or severe AS in patients ≥75 years of age was as high as 2.8% (23). The inverse relationship between LV wall stress and ejection fraction may at least partly explain LV systolic dysfunc-

tion (24), and one-quarter of all patients with AS have LV systolic dysfunction (25).

AS progression in our study was illustrated by an annual AVA decrease by ± 0.10 cm² to ± 0.24 cm², and is in keeping with the ± 0.1 cm² average annual AVA decrease reported in previous studies (8,9). The need for AVR at 1-year follow-up was higher than previously reported in patients with asymptomatic severe AS (13% vs. 5% to 9%) (8,26) or moderate AS and preserved LV function (13% vs. 4% to 8%) (15,16,18,27). Although the decision to intervene could not be determined from this retrospective study (e.g., clinical HF, progression of AS, progressive symptoms), it might suggest accelerated clinical deterioration in patients with moderate AS and LV dysfunction.

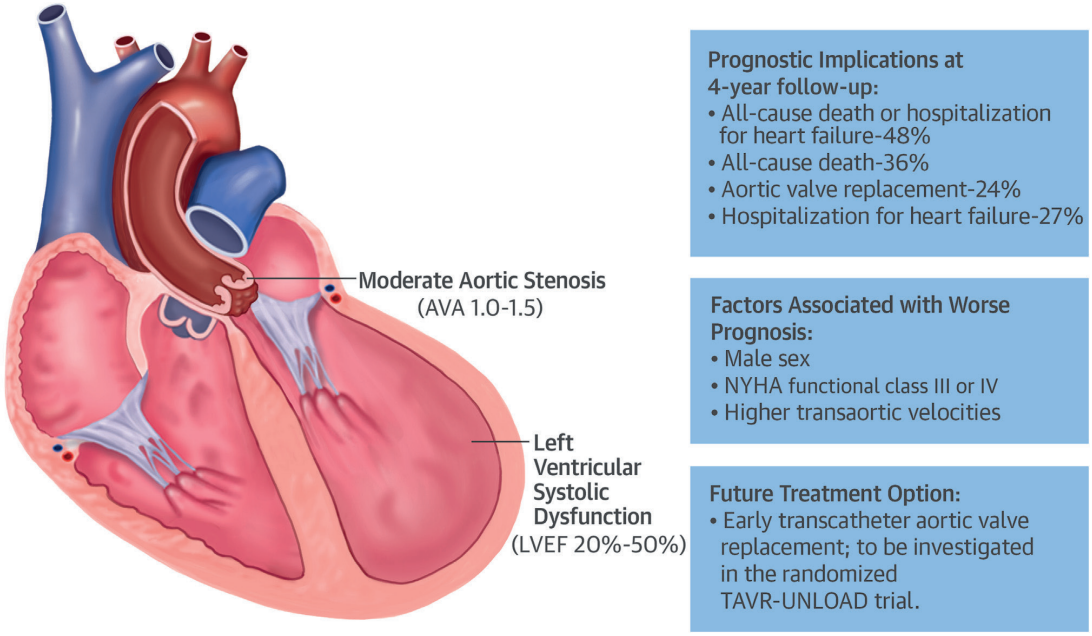

Figure 8. Moderate aortic stenosis and LV systolic dysfunction. Patients with left ventricular (LV) systolic dysfunction (left ventricular ejection fraction [LVEF] 20% to 50%) and concomitant moderate aortic stenosis (aortic valve area [AVA] 1.0 to 1.5 cm²) are at high risk for clinical events, including all-cause death and hospitalization for heart failure. Currently, aortic valve replacement is not indicated in these patients, although they may receive benefit. This premise will be studied in the randomized TAVR-UNLOAD (Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients with Advanced Heart Failure) trial.

The rates for all-cause death and hospitalization for HF were 25% and 26% respectively at 3-year follow-up. In recent large HF trials enrolling symptomatic patients with an LVEF ≤35%, 3-year rates for HF admissions and all-cause death were <20% and 25%, respectively (28). The higher event rates in the current study might suggest that the presence of moderate AS in patients with LV systolic dysfunction negatively affects overall prognosis.

Similar to HF studies, symptoms but not LVEF were a strong predictor for clinical events (29,30). Patients in NYHA functional class III or IV had significantly more events than patients in NYHA functional class II or I (primary composite endpoint 84% vs. 54% and 45%, respectively; $p < 0.001$). Patients admitted for HF at the time of the index echocardiogram had a 2-fold higher 1-year event rate, including significantly more admissions for HF (43% vs. 4%; $p < 0.001$).

The true effect of moderate AS in patients with LV systolic dysfunction remains unknown, although indirect evidence suggests survival benefit with AVR. In the TOPAS (True or Pseudo Severe Aortic Stenosis) observational cohort study, an AVA <1.2 cm^2 as opposed to AVA <1 cm^2 was associated with mortality in medically treated patients with low-flow, low-gradient AS (31–34). A retrospective analysis from the Duke Echocardiographic Database reported a mortality benefit associated with AVR (with or without concomitant CABG) for moderate AS in patients with LV systolic dysfunction (35). Finally, moderate prosthesis/patient mismatch after AVR, which generally corresponds to residual moderate AS, has been associated with increased risk of early and late mortality in patients with LV systolic dysfunction (36–38). In aggregate, patients with moderate AS and LV systolic dysfunction might be more vulnerable to the increased LV afterload imposed by AS and, thus, benefit from AVR. The high event rate in these patients warrants further research and may justify the exploration of early TAVR in this population. Indeed, TAVR has become an attractive, minimally invasive alternative to SAVR for patients with severe AS and intermediate or greater surgical risk (39–43). Early TAVR may provide additional afterload reduction and thus affect clinical outcome in patients with moderate AS and LV systolic dysfunction. This premise will be studied in the randomized TAVR UNLOAD (Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients with Advanced Heart Failure) trial (NCT02661451) (44).

Study limitations

The retrospective design of the study might introduce selection bias. Although all patients in our study shared the common denominator of moderate AS and LV systolic dysfunction, the population was heterogeneous. There were multiple underlying causes of LV systolic dysfunction, and there were diverse therapeutic regimens in this multinational population. Not all patients were necessarily treated with optimal HF therapy. This might be partly explained by the fact that one-quarter of patients were in NYHA functional class I and might never have had HF symptoms.

Furthermore, we elected to define moderate AS according to the parameters (AVA, mean gradient, and peak velocity) and cut-off values proposed in the guidelines (13). Using AVAi to determine AS severity might have reclassified some patients with large BSA from moderate to severe AS (if AVAi is ≥0.6 cm^2/m2). Conversely, patients with small BSA might have been reclassified from mild AS (based on AVA) to moderate AS (based on AVAi). However, 1 of the important limitations of AVAi is that it may overestimate AS severity in obese patients. In this regard, one-half of the patient population with AVAi <0.6 cm^2/m^2 in our series had a body mass index >30 kg/m^2 versus 20% of patients with AVAi ≥0.6 cm^2/m^2. Furthermore, a recent study suggested using lower cut-off values for AVAi to define severe AS (45). Hence, further studies are needed to refine the method of indexation of AVA in patients with AS to achieve more accurate estimation of AS severity. Nevertheless, this database likely reflected real-life practice and underscored the complexity of AS diagnosis and HF treatment. A propensity-matched analysis versus patients with LV dysfunction without AS could further clarify the added burden of moderate AS in patients with LV dysfunction.

Finally, the decision to proceed with AVR in our study was undertaken by the treating physician and might reflect center-specific practices. DSE was performed in 11% of patients. It may be possible that we failed to include more patients with pseudo-severe (and thus moderate) AS because the treating physi-

cian did not perform a DSE. It is also possible that DSE interpretation was incorrect and patients had true severe AS rather than moderate AS. Patients in whom the DSE revealed true severe AS were not included because low-flow, low-gradient severe AS falls beyond the scope of this retrospective study. Although this retrospective study reflected contemporary practice in 4 academic institutions, some patients might have had severe AS based on indexed AVA and might have benefitted from AVR at an earlier stage.

CONCLUSIONS

Patients with concomitant moderate AS and LV systolic dysfunction are at high risk for clinical events. Further studies are needed to determine if earlier AVR in these patients might improve clinical outcome.

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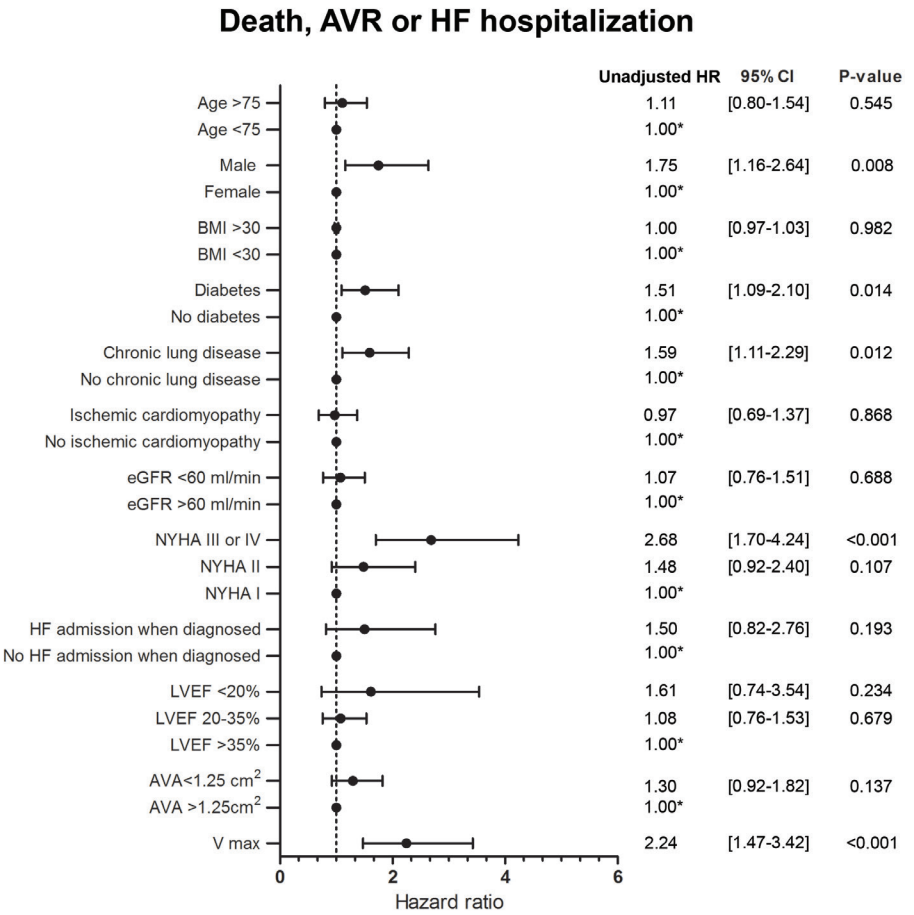
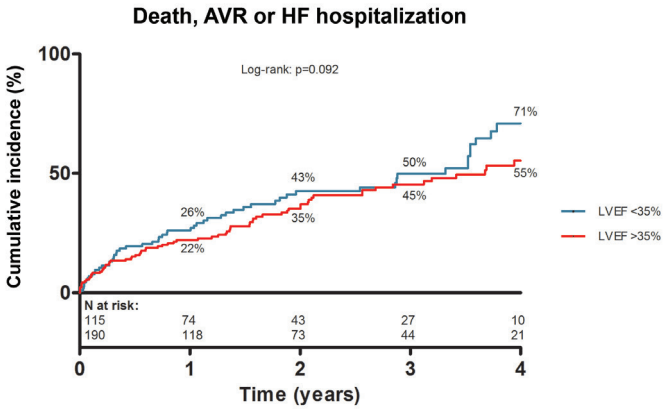
SUPPLEMENTAL MATERIAL

	Medically treated (n=159)			AVR* (n=13)		
	Index	**Follow-up**	**P-value**	**Index**	**Follow-up**	**P-value**
LVEF (%)	38 ± 9	39 ± 11	0.226	39 ± 7	39 ± 12	0.894
AVA (cm²)	1.24 ± 0.16	1.14 ± 0.25	<0.001	1.23 ± 0.14	1.00 ± 0.22	0.004
Vmax (m/s)	2.5 ± 0.4	2.6 ± 0.5	0.001	2.8 ± 0.5	3.1 ± 0.6	0.074
PG (mmHg)	26 ± 8	29 ± 12	<0.001	32 ± 8	39 ± 14	0.085
MG (mmHg)	14 ± 4	16 ± 7	<0.001	18 ± 4	22 ± 8	0.127

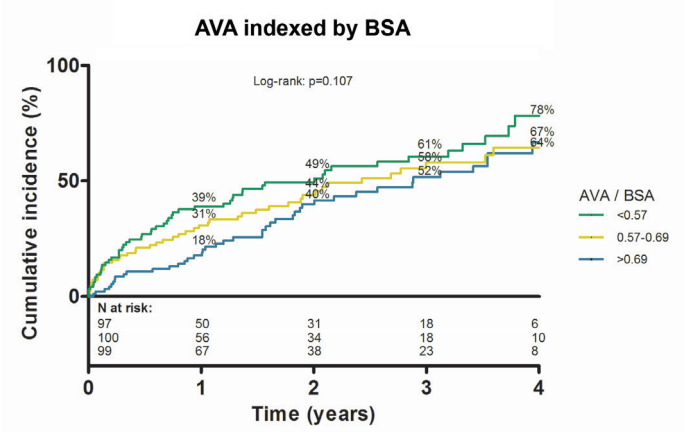
Supplemental table 1. Evolution of echocardiographic parameters for patients with and without AVR. Variables are displayed as mean ± SD. Median time between index and follow-up echo was 541 days (IQR [337-890]) for medically treated patients and 467 (IQR [315-937]) for patients with AVR. *Follow-up echocardiograms were before AVR. Abbreviations: AVA = Aortic Valve Area; MG = mean gradient; LVEF = left ventricular ejection fraction; PG = peak gradient; Vmax = peak aortic jet velocity.



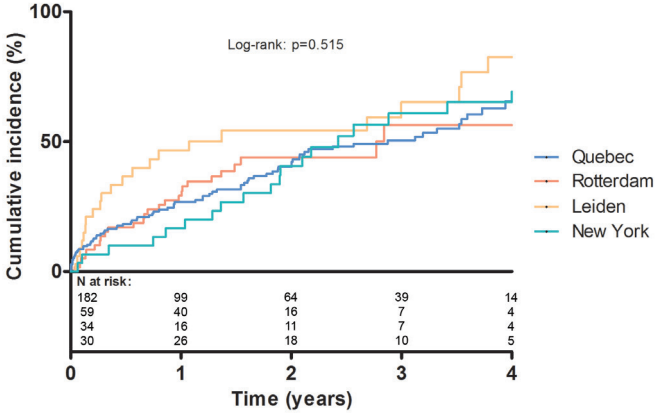
Supplemental figure 1. Forest plot of hierarchical univariate cox-regression analysis. A two-step hierarchical univariate cox-regression model was conducted to evaluate predictors for the primary composite endpoint – All-cause death, AVR or HF hospitalization. *reference category. Abbreviations: AVA = Aortic valve area, AVR = Aortic valve replacement, BMI = Body mass index, CI = Confidence interval, eGFR = Estimated glomerular filtration rate, HF = Heart failure, HR = Hazard ratio, LVEF = Left ventricular ejection fraction, NYHA = New York Heart Association, V max = Peak aortic jet velocity.



Supplemental figure 2. Composite of all-cause death, AVR or HF hospitalization stratified by LVEF. Cumulative incidence curves (Kaplan-Meier) stratified by LVEF ≤35% and >35%. Prognosis was similar between both groups throughout follow-up.



Supplemental figure 3. Composite of all-cause death, AVR or HF hospitalization according to tertiles of indexed AVAi. Cumulative incidence curves (Kaplan-Meier) stratified by tertiles of AVAi. Prognosis was similar across the three tertiles. Abbreviations: AVAi = Indexed aortic valve area.



Supplemental figure 4. Composite of all-cause death, AVR or HF hospitalization stratified by institutions. Cumulative incidence curves are stratified for the respective participating institutions.

CHAPTER XVIII

Clinical outcomes of the Lotus valve in patients with bicuspid aortic valve stenosis. An analysis from the RESPOND study

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Submitted

ABSTRACT

Aims

Patients with bicuspid valves represent a challenging anatomical subgroup for transcatheter aortic valve implantation (TAVI). This analysis evaluated the clinical outcomes of the fully repositionable and retrievable Lotus Valve TAVI System in patients with bicuspid aortic valves enrolled in the RESPOND post-market registry.

Methods and Results

The prospective, open-label RESPOND study enrolled 1014 patients at 41 centres in Europe, New Zealand, and Latin America; 31 (3.1%) of whom had bicuspid aortic valves. The mean age in the bicuspid patient cohort was 76.4 years, 64.5% were male, and the baseline STS score was 6.0±10.2. Procedural success was 100%, with no cases of malpositioning, valve migration, embolization, or valve-in-valve. Repositioning was attempted in 10 cases (32.3%). There was one death (3.2%) and one stroke (3.2%) at 30-day follow-up. Mean AV gradient was reduced from 48.7±17.0 mmHg at baseline to 11.8±5.1 mmHg at hospital discharge ($P<0.0001$); mean effective orifice area (EOA) was increased from 0.6±0.2 cm^2 to 1.7±0.4 cm^2 ($P<0.0001$). There were no cases of moderate or severe paravalvular leak (PVL) adjudicated by the core laboratory; 4 subjects (13.8%) had mild PVL, 5 (17.2%) had trace PVL. The rate of pacemaker (PM) implantation for PM-naïve patients was 22.2% (6/27).

Conclusions

Patients with bicuspid valves represent a challenging anatomical subgroup for TAVI. Data from the RESPOND registry demonstrate good clinical and echocardiographic outcomes with the repositionable Lotus valve in these patients through 30 days postimplantation. Patients with bicuspid valves represent a challenging anatomical subgroup for transcatheter aortic valve implantation (TAVI). This analysis evaluated the clinical outcomes of the fully repositionable and retrievable Lotus Valve TAVI System in patients with bicuspid aortic valves enrolled in the RESPOND post-market registry.

INTRODUCTION

Bicuspid valves are one of the most common congenital aortic valve anomalies, present in up to 2% of the population (1,2). Compared to tricuspid valves, bicuspid valves have a larger annulus perimeter, an asymmetrical valve orifice, and more heavily calcified leaflets/raphe (3,4). Patients with a bicuspid aortic valve are at increased risk for aortic stenosis, aortic dilation, aneurysm, and dissection (3,4). While TAVI is an established treatment option for patients with symptomatic aortic stenosis who are at high risk for surgical valve replacement (5,6), patients with bicuspid valves have been excluded from most TAVI clinical trials and bicuspid-TAVI data are limited. Demonstrating safety and efficacy in bicuspid valves is essential for TAVI devices, particularly if TAVI is to be extended into younger populations in whom bicuspid anatomy is more prevalent.

Previous data have consistently shown worse outcomes following TAVI in bicuspid anatomy, including increased paravalvular leak (PVL), non-uniform/non-circular valve deployment, reduced procedural success, device migration/embolisation, malfunction, and annular rupture, (7-13). The Boston Scientific Lotus valve has several features which may be of benefit in patients with bicuspid anatomy, including a sealing skirt to reduce PVL, deployment via gradual mechanical expansion, and full retrievability and repositionability. The REPRISE II (REpostionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus Valve System: Evaluation of Safety and Performance) (14), and the REPRISE III (Repositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus Valve System – Randomized Clinical Evaluation) (15) trials excluded patients with bicuspid valves.

The RESPOND study evaluated TAVI with the Lotus Valve when used in routine clinical practice, including in patients with bicuspid aortic valve anatomy. This analysis evaluates outcomes with Lotus in patients with bicuspid aortic valves.

METHODS

Study Design and Patient Selection

The RESPOND (Repositionable Lotus Valve System – Post Market Evaluation of Real World Clinical Outcomes) Study is a prospective, open label, single arm, multi-center, observational post-market registry from 41 centers in Europe, New Zealand, and Latin America. The study design has been previously described (16). Data collection occurred at baseline, index procedure, discharge and at 30 days post-procedure for all enrolled subjects.

The protocol was approved by the locally appointed institutional review boards/ethics committees, and the study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the ethical principles outlined in the Declaration of Helsinki. The study was registered with ClinicalTrials.gov (NCT 02031302). All patients gave written informed consent.

Device and Procedural Details

The Lotus Valve System™ consists of a bioprosthetic aortic valve premounted on a preshaped delivery

catheter. Novel features of the Lotus Valve System include an Adaptive Seal™ designed to mitigate PVL, controlled mechanical expansion, and the ability to fully recapture or reposition the valve prior to release. Detailed descriptions of the Lotus Valve System have been previously published (17-19).

Outcomes Measures

The primary endpoint for RESPOND was all-cause mortality at 30 days and 1 year in the intent to treat population. Secondary endpoints included in-hospital mortality, the composite of allcause mortality and disabling stroke at 30 days and 1 year, and grade of paravalvular aortic valve regurgitation at discharge and 1 year. Major clinical events (i.e. all-cause mortality and stroke events) were adjudicated by an Independent Medical Reviewer (IMR). Baseline and follow-up echocardiography studies were evaluated by an independent core laboratory (Cardialysis Core Laboratory, Rotterdam, Netherlands).

For this sub-analysis, the preliminary identification of bicuspid anatomy was site-reported. The echo core laboratory then provided an initial characterization of bicuspid anatomy using Sievers' valve classification scheme to define each valve as Type 0, Type 1, or Type 2 (20) (Figure 1). Each identified bicuspid valve was further validated via systematic review of CT angiograms. No specific guidance for the selection of valve size in bicuspid valves was provided and the final decision was at the discretion of the operator. This is the first registry to date to employ the use of an independent clinical event committee as well as to assess both CT and echo data for bicuspid valve validation and characterization.

Patient Characteristic	Bicuspid Cohort N=31	Non-bicuspid Cohort N=965	P-value
Age. years	76.4 ± 7.9 (31)	80.9 ± 6.4 (965)	<0.001
Gender. male	64.5 (20/31)	48.7 (470/965)	0.083
BMI (kg/m2)	28.1 ± 4.91 (30)	26.6 ± 4.82 (956)	0.093
STS score	6.0 ± 10.15 (28)	5.9 ± 6.74 (821)	0.948
EuroSCORE 20II	6.1 ± 7.52 (29)	8.0 ± 8.38 (821)	0.233
Diabetes mellitus. medically treated	16.1 (5/31)	22.5 (217/965)	0.403
History of COPD	9.7 (3/31)	15.7 (151/963)	0.458
NYHA Class III or IV	66.7 (20/30)	69.6 (623/895)	0.731
History of hypertension	71.0 (22/31)	79.4 (760/957)	0.254
Coronary artery disease. history	25.8 (8/31)	57.1 (550/964)	0.001
Prior PCI	12.9 (4/31)	30.4 (292/962)	0.037
Prior CABG	3.2 (1/31)	12.6 (122/965)	0.163
Prior implanted pacemaker	12.9 (4/31)	13.4 (129/965)	0.163
Atrial fibrillation. history	19.4 (6/31)	24.1 (232/964)	0.545
Porcelain aorta	6.5 (2/31)	4.3 (41/960)	0.394
Hostile chest/unfavourable chest wall anatomy	0.0 (0/31)	1.0 (10/964)	1.000
Cerebrovascular accident. history	16.1 (5/31)	9.3 (89/962)	0.205
Transient ischaemic attack. history	0.0 (0/31)	7.6 (73/958)	0.161

Table 1. Baseline Patient Characteristics. Values are mean ± SD (N) or % (n/N).

RESULTS

Study Participants and Baseline Characteristics

The RESPOND post-market registry enrolled 1014 patients between May 2014 & February 2016; 31 of the 996 patients implanted with a Lotus Valve were identified as having bicuspid anatomy. Most baseline characteristics for bicuspid and tricuspid patients from RESPOND were similar. Significant baseline differences existed for average age (76.4±7.9 years bicuspid vs 80.9±6.4 years tricuspid; P<0.001), history of coronary artery disease (CAD) (25.8% bicuspid vs 57.1% tricuspid; P<0.001), and percutaneous coronary intervention (PCI) (12.9% bicuspid vs 30.4% tricuspid; P<0.05) (Table 1). The majority of the bicuspid patients (71.0% [22/31]) had Sievers Type 1 valve anatomy (20 L-R, 2 R-N). 16.1% (5/31) had Type 0 valves, 3.2% (1/31; 1 R-N) had Type 2 valves, and 9.7% (3/31) were unable to be classified due to scan quality.

Core lab adjudicated baseline echocardiography was significantly different between the two groups. The mean effective aortic orifice area (EOA) was 0.6±0.2cm² for bicuspid and 0.7±0.2cm² for tricuspid (P=0.008) and the mean AV gradient was 48.7±17.0mmHg for bicuspid and 37.6±15.3mmHg for tricuspid (P<0.001). There were no significant differences in aortic regurgitation at baseline (Severe AR: 3.7% for bicuspid, 2.2% for tricuspid; Moderate AR: 18.5% for bicuspid, 14.2% for tricuspid; None-Mild AR: 77.8% for bicuspid, 83.6% for tricuspid; P=NS for all). Site-reported aortic valve calcification was similar for patients with bicuspid valves and patients with tricuspid aortic valves (Severe: 38.7%

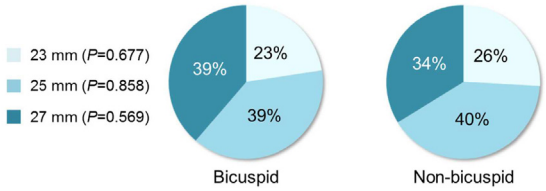

Figure 2. Lotus valve sizing. Distribution of valve sizes within the bicuspid and tricuspid patient populations was similar.

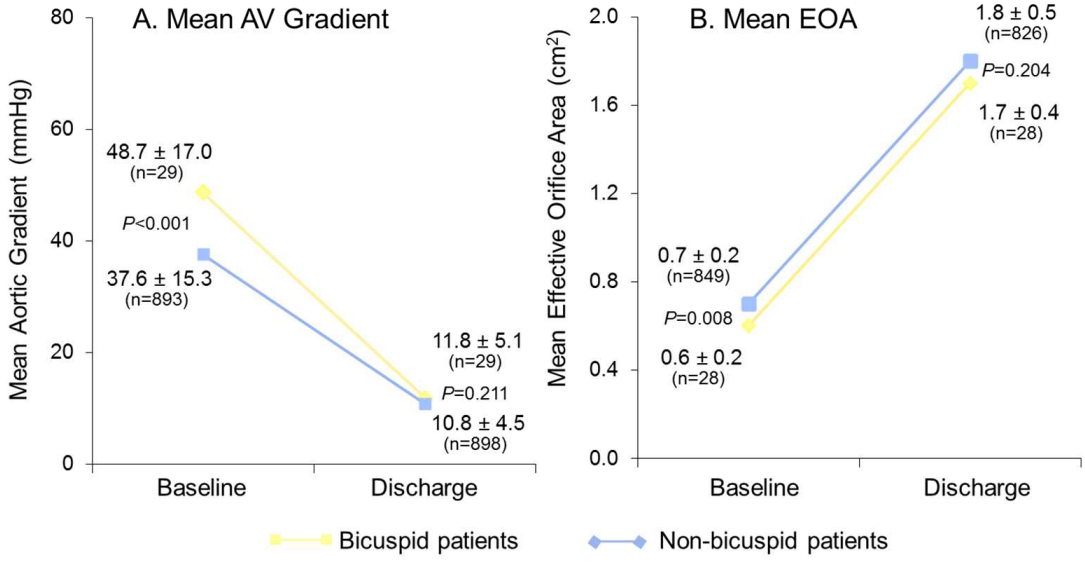

Figure 3. Mean Aortic Valve Gradient and Effective Orifice Area. Bicuspid and tricuspid patients both demonstrated a significant change in mean aortic gradient and EOA from baseline to discharge. Baseline mean aortic gradient was different for the bicuspid and tricuspid cohorts with no difference between groups at discharge. Baseline and discharge measurements between the groups were not different for mean EOA. Data is core-lab adjudicated.

vs 36.4%; Moderate: 45.2% vs 35.3%, Mild: 9.7% vs 17.4%; Unknown/Not reported: 6.5% vs 10.9%; bicuspid vs tricuspid P=NS for all). Site-reported aortic annulus diameter (23.8±2.4mm for bicuspid, 22.8±4.8mm for tricuspid; P=0.095) and LVEF (50.9±15.3% for bicuspid, 54.8±13.0% for tricuspid; P=0.112) were similar for both groups. There were 11 (35.4%) aortic root aneurysms reported in the bicuspid cohort of the RESPOND registry.

Procedural Success and Details

Both the bicuspid and tricuspid cohorts demonstrated high rates of procedural success. Predilation was performed significantly more often in the bicuspid cases than in the tricuspid cases (80.0% [24/30] for bicuspid, 53.0% [500/943] for tricuspid; P = 0.0035). Correct positioning of a single prosthetic valve in the proper anatomical location occurred in 100% of the bicuspid cases - there were no cases of migration, embolization, or deployment of a second valve. Repositioning was attempted in 10 bicuspid patients (32%) and 299 tricuspid patients (31%). If attempted, repositioning was successful in 9 of 10 attempts (90%) for bicuspid patients and in 287 of 299 attempts (96.0%) for tricuspid patients. The bicuspid and tricuspid cohorts had a similar distribution of valve sizes (27mm: 39% for bicuspid, 34% for tricuspid; 25mm: 39% for bicuspid, 40% for tricuspid; 23mm: 23% for bicuspid, 26% for tricuspid; P=NS for all). (Figure 2) Haemodynamic Performance The mean AV gradient was statistically different between bicuspid and tricuspid patients at baseline (48.7±17.0mmHg for bicuspid, 37.6±15.3mmHg for tricuspid; P<0.001) but was similar at discharge (11.8±5.1mmHg for bicuspid, 10.8±4.5mmHg for tricuspid; P=0.211). The mean EOA measurements were also different at baseline and similar at discharge between the groups; both cohorts demonstrated a significant increase in effective orifice area (Baseline EOA: 0.6±0.2cm² for bicuspid, 0.7±0.2cm² for tricuspid; P=0.008. Discharge EOA: 1.7±0.4cm² for bicuspid, 1.8±0.5cm² for tricuspid; P=0.204). (Figure 3) At hospital discharge, PVL was not significantly different for bicuspid vs tricuspid patients (Mod/Severe PVL: 0% for bicuspid, 0.3% for tricuspid; Mild PVL: 13.8% for bicuspid, 7.5% for tricuspid; Trace PVL: 17.2% for bicuspid, 10.9% for tricuspid; None: 69% for bicuspid, 81.2% for tricuspid; P=NS). (Figure 4)

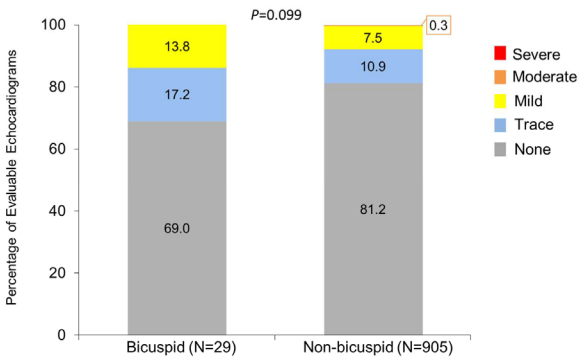

Figure 4. Paravalvular Aortic Regurgitation at Discharge. No severe PVL in either bicuspid or tricuspid group. 86.2% of the bicuspid cohort and 92.1% of the tricuspid cohort had none/trace PVL. Data is core-lab adjudicated.

Safety

All-cause mortality at 30 days was not different between bicuspid and tricuspid groups (3.2% for bicuspid, 2.2% for tricuspid; P=0.509). There were no significant differences between other principal safety outcomes at 30 days such as all stroke (3.2% for bicuspid, 3.0% for tricuspid; P=1.000), major vascular complications (6.5% for bicuspid, 2.8% for tricuspid; P=0.231), and pacemaker implantation (22.2% in pacemaker-naïve patients for bicuspid, 35.3% for tricuspid; P=0.162). (Table 2)

30-Day Outcomes	Bicuspid N=31	Non-bicuspid N=965	P-value
All-cause mortality	3.2 (1/31)	2.2 (21/955)	0.509
Cardiovascular	3.2 (1/31)	2.0 (19/955)	0.476
Non-cardiovascular	0.0 (0/31)	0.2 (2/955)	1.000
Stroke	3.2 (1/31)	3.0 (29/955)	1.000
Disabling	3.2 (1/31)	2.2 (21/955)	0.509
Non-disabling	0 (0/31)	0.8 (8/955)	1.000
All-cause mortality and disabling stroke	6.5 (2/31)	4.0 (38/955)	0.361
Vascular Complications	12.9 (4/31)	8.6 (82/955)	0.339
Major	6.5 (2/31)	2.8 (27/955)	0.231
Life-threatening or disabling bleeding	6.5 (2/31)	2.1 (20/955)	0.150
PM Implantation for PM-Naïve Patients	22.2 (6/27)	35.3 (292/828)	0.162
MI (>72 hours post-procedure)	0.0 (0/31)	0.6 (6/955)	1.000
Acute Kidney Injury (Stage 2 or 3)	3.2 (1/31)	2.5 (24/955)	0.555

Table 2. Principal Safety Results at 30 Days.

Undersizing in Bicuspid Anatomy

Annulus diameter measurements were performed by site and valve sizing was determined at the discretion of the operator. Of the 31 patients with bicuspid anatomy, four had significant (>10%) undersizing by annulus diameter. PVL and haemodynamic results in these 4 patients were good. (Table 3)

Patient	Valve Size (mm)	Area derived annulus diameter (mm)	Mean Aortic Gradient (mmHg)		PVL
			Baseline	30 Days	
1	27	30.0	61.6	NR	NR
2	27	31.6	53.6	12.9	Mild
3	25	28.0	48.2	15.8	None
4	27	30.0	22.9	12.0	Trace

Table 3. Four cases of undersizing in bicuspid valves.

DISCUSSION

The principal finding of this study is that outcomes for patients with bicuspid aortic valves who underwent TAVI with the Lotus Valve in the "real-world" RESPOND registry were comparable to those with tricuspid aortic valves receiving the Lotus Valve. The bicuspid cohort was significantly younger, which aligns with other descriptions of aortic stenosis in bicuspid valves (1), and the bicuspid cohort presented with significantly less coronary artery disease. There was no significant difference in clinical outcomes between bicuspid and tricuspid patients, including mortality, stroke, bleeding, vascular complications, and acute kidney injury. Device success in bicuspid patients was 100%, with no cases of migration, embolization, placement of a second valve, or annular rupture. Consistent with the low rates of PVL with Lotus in tricuspid anatomy, bicuspid patients in RESPOND had 0% moderate/severe PVL and only 13.8% mild PVL, as well as good haemodynamics.

Challenges of TAVI in Bicuspid Anatomy

Due to the high level of calcification and eccentric geometry in patients with bicuspid anatomy, TAVI in bicuspid valves may be subject to an increased risk of complications related to irregular and incomplete expansion of the prosthetic valve (9). Asymmetrical expansion of valves has been observed as high as 38% with the S3 valve in bicuspid anatomy (10) and Zegdi et al.describes noncircular stent deployment as 81% more frequent in bicuspid vs tricuspid aortic valves (11). Non-circular or irregular valve expansion may impact valve hemodynamics and durability. Valve haemodynamics following TAVI, including mean gradient and effective orifice area, were no different between bicuspid and tricuspid valves in RESPOND, despite a range of eccentricity from 1.11-1.48 in the bicuspid group. (Supplementary Table 1) This similarity may be attributed to the independent mobility of the Lotus valve leaflets. The Lotus valve is designed such that the leaflets are not sutured to the valve frame, and are therefore not affected by noncircular valve expansion. Furthermore, heavy calcification and eccentricity of the native annulus increases the risk of device malapposition and consequently of PVL. In a comparative analysis from the German TAVI Registry of bicuspid vs tricuspid valves, the risk for moderate or greater aortic regurgitation (AR) was higher in patients with bicuspid anatomy receiving CoreValve or Sapien (12). Mylotte et al similarly reported a high incidence of post-implant AR in 139 bicuspid patients undergoing TAVI with Sapien XT and CoreValve (AR grade ≥2 was 28.4%) (13).

In tricuspid anatomy, the Lotus Valve has low rates of PVL due to the Adaptive Seal feature. This seal reduces PVL by conforming to irregular anatomic surfaces, which may be a crucial attribute for minimizing PVL in bicuspid anatomy. In this analysis PVL was similar between tricuspid and bicuspid patients; there were no cases of moderate or severe PVL in patients with bicuspid valves, and even mild PVL was seen in only 13.8%. This result is consistent with the findings of Yoon et al for PVL with current generation TAVI in bicuspid valves (8). Device success is lower overall for bicuspid TAVI-patients as compared to tricuspid TAVI patients (8).

Bicuspid patients are at increased risk for malfunctioning valves post-TAVI due to high leaflet co-aptation, leaflet fusion, as well as extensive and asymmetric calcification (7). The Lotus Valve is fully repositionable and retrievable, allowing precise positioning in asymmetric anatomy, and avoiding risk of device migration or embolization. Deployment via gradual mechanical expansion also minimizes the risk of annular rupture. Despite frequent aortopathy (35.4% [11/31] of patients with bicuspid valves in RESPOND had aortic root aneurysms), no cases of dissection were seen with the Lotus Valve in RESPOND. The data from this subanalysis support these potential advantages of the Lotus Valve for bicuspid patients as there were no cases of migration, embolization, deployment of a second valve, or annular rupture.

Valve Sizing in Bicuspid Anatomy

For the RESPOND registry, sizing of the valve was at the discretion of the implanter. Some clinicians have hypothesized that routine undersizing may be beneficial in bicuspid anatomy, allowing fixation and sealing within the leaflets, with more complete and symmetrical expansion of the valve frame to optimize haemodynamics and potentially enhance long-term durability. In this analysis four patients received valves that had >10% undersizing; all four had good outcomes with respect to PVL and valve haemodynamics. Other studies have shown a tendency to oversize TAVI devices in bicuspid anatomy in an effort

to circularize the annulus, prevent malpositioning, and reduce PVL even though oversizing may increase the risk of rupture (8). The combination of controlled mechanical expansion and the Adaptive Seal of the Lotus Valve may provide a benefit in addressing these challenges. Specific sizing for bicuspid anatomy with the Lotus Valve will require further investigation.

Study Limitations

The primary limitation of this study is the small size of the analysis population. Additionally, RESPOND is a single-arm registry, and not a randomized study. Aortic valve calcification and preliminary identification of bicuspid anatomy were site-reported, although central CT analysis was used to confirm bicuspid anatomy and echocardiography data was analyzed by an independent core laboratory. In RESPOND, 3% of patients were identified as having bicuspid aortic valve stenosis; however, other studies have shown an incidence of approximately 20% (2). It is possible that in this study, and others, that initial identification via echo failed to capture all patients with functional bicuspid anatomy, underestimating the true number of bicuspid patients in the TAVI population. At the time of this study, the largest available Lotus Valve was 27mm, which limits the results to patients with smaller annular diameters.

Conclusions

TAVI with the Lotus valve in patients with bicuspid aortic valve anatomy treated within the RESPOND registry was associated with good procedural, clinical, and haemodynamic outcomes.

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SUPPLEMENTAL MATERIAL

Patient	Bicuspid type	Aortic Valve Area (mm2)	Annulus Maximum Diameter (mm)	Annulus Minimum Diameter (mm)	Eccentricity Index	Aortic Valve Calcification
1	Type 1 L-R	562.3	31.4	23.2	1.35	None
2	Type 1 L-R	578.5	32.2	22.6	1.42	Mild
3	Type 2 R-N	550.3	28.9	24.9	1.16	Mild
4	Type 1 L-R	549.5	28.1	24.4	1.15	Moderate
5	Type 1 L-R	520.5	28.5	22.9	1.24	Moderate
6	Type 1 L-R	413.2	26.0	20.8	1.25	Moderate
7	Type 0	601.0	32.7	23.2	1.41	Moderate
8	Type 1 L-R	507.3	28.4	22.8	1.25	Moderate
9	Type 1 L-R	523.0	30.3	21.5	1.41	Moderate
10	Type 0	488.4	29.9	21.0	1.42	Moderate
11	Type 1 L-R	372.0	26.0	18.3	1.42	Moderate
12	Type 0	399.4	23.6	21.3	1.11	Moderate
13	Type 1 L-R	430.0	24.8	21.8	1.14	Moderate
14	Type 1 R-N	305.4	21.8	17.7	1.23	Moderate
15*	Type 1 L-R	705.8	33.8	26.3	1.29	Severe
16	Type 0	394.7	26.9	18.8	1.43	Severe
17	Type 1 L-R	423.1	25.3	21.0	1.20	Severe
18	Type 1 L-R	380.7	26.7	18.1	1.48	Severe
19	Type 1 L-R	429.3	28.2	19.2	1.47	Severe
20	Type 1 L-R	537.8	30.7	22.7	1.35	Severe
21	Type 1 L-R	521.7	28.1	23.4	1.20	Severe
22	Type 0	486.9	27.9	22.2	1.26	Severe
23*	Type 1 L-R	536.0	28.7	23.9	1.20	Severe
24	Type 1 L-R	476.6	25.2	23.8	1.06	Severe
25	Type 1 R-N	571.7	29.1	25.2	1.15	Severe
26*	Type 1 L-R	661.6	30.5	27.1	1.13	Severe
27	Type 1 L-R	545.2	28.7	24.2	1.19	Severe
28	Type 1 L-R	484.3	28.3	22.2	1.27	Severe
29	UNK	UNK	UNK	UNK	UNK	UNK
30	UNK	UNK	UNK	UNK	UNK	UNK
31*	UNK	UNK	UNK	UNK	UNK	UNK

Supplemental table 1. CT Measurements for Patients with Bicuspid Valves *Indicates case where Lotus Valve was undersized.

Epilogue

Summary and discussion

In the past decade, transcatheter aortic valve implantation (TAVI) has matured to the mainstay treatment for patients with severe symptomatic aortic stenosis (18). The technology was first tested and approved in patients who were inoperable or at high risk for death or complications with surgical aortic valve replacement (SAVR) (3-5), but expanded to intermediate risk patients(6-8). Importantly the multidisciplinary heart team that includes cardiac surgeons, interventional cardiologists, imaging specialists, geriatricians and anesthesiologists should determine the optimal treatment strategy for elderly patients with severe AS (17).

Valve manufacturers are continuously improving their designs in order to improve success rate and safety of the procedure. In the process, TAVI is becoming easier to use and the workflow is fastened and a 'same-day-discharge' scenario appears feasible.

Over the past decade different TAVI platforms have become commercially available and offers the physician a tailored approach to treat severe aortic stenosis in patients at elevated operative risk.

Pre-procedural multi-modality imaging is essential for proper patient and device selection. In particular the multi-slice computed tomography of the arterial tree and aortic valve provides crucial information. Chapter 1 dives into the current landscape of new-generation transcatheter heart valves and touches upon sizing strategies (19). The Lotus valve is the only system that is deployed by mechanical expansion. Lotus is the only platform with true reposition and retrieval ability. These unique features make it attractive in complex anatomies where there is insecurity about the valve size or with exuberant amounts of calcium in the aortic root. Chapter 2 gives a detailed description of the Lotus valve concept and runs through the steps of implantation.

Early reports of new-generation transcatheter heart valves show excellent performance (20-22). Obviously, the diverging concepts have their inherent advantages and disadvantages, which are discussed in this thesis.

Part I – Conduction disorders

As with surgical aortic valve replacement, TAVI is associated with the occurrence of new - and aggravation of existing - conduction disorders.

The anatomical landing zone of a transcatheter heart valve lies beneath the native aortic valve annulus in the left ventricular outflow and in close proximity to the cardiac conduction system (10,23,24). Sufficient radial expansion is a prerequisite for stability and optimal performance of the bioprosthesis. As such, radial force is exhibited to the conducting bundles and might inflict damage. The fate of these acquired conduction disturbances are subject of intense research.

It is noteworthy that most of the new conduction disorders are already observed during minimal LVOT interaction by guidewires and catheters, and thus before the bioprosthesis is de facto deployed. The majority of these newly developed conduction disturbances may resolve, although others persist or even deteriorate after the valve deployment (25). The fate of these conduction abnormalities has not been completely elucidated but may affect patient safety and hospitalization policy. TAVI practice is moving towards earlier discharge. This may pose challenges in patients who developed conduction disturbanc-

es during or after TAVI. In Chapter 3 we hypothesized that the interventricular conduction time (i.e. QRS-duration) may represent a valuable predictor for permanent conduction disorders by retrospective assessments of daily ECG's following TAVI. We discovered that patients with a stable small QRS-duration may develop transient conduction blocks but almost always completely recovered and thus did not require a permanent pacemaker. Conversely, patients with prolonged QRS-prolongation at baseline or persistent after the procedure were at risk for life-threatening conduction blocks and need for permanent pacing. The daily ECG helped thus identify the patients whose conduction was recovering and became eligible for an early discharge from the hospital. This finding warrants further prospective validation in large cohorts.

Up to 20% of patients have a right bundle branch block (RBBB) before the TAVI procedure and are at particularly high risk for the development of high-grade AV block and need for permanent pacing (26). In Chapter 4 we studied whether transcatheter bioprosthesis selection could contribute to avoid the need for permanent pacing after TAVI in these patients (27). Although all devices were associated with more need for pacemakers in these patients with RBBB, the mechanically expanded Lotus valve was associated with the highest risk. This finding underlines the necessity to take this interplay into account before selecting a transcatheter heart valve rather than using the same device in all clinical scenarios.

Transcatheter heart valves rely on radial expansion to anchor within the aortic root. Current sizing of transcatheter heart valves typically considers the dimensions at the level of the basal aortic valve annulus. However, the conduction system surfaces below the annulus in the left ventricular outflow tract (LVOT). The LVOT is often smaller than the annulus. Consequently, sizing relative to the annulus might thus often result in more dramatic oversizing relative to the LVOT dimensions. Chapter 5 confirms that oversizing relative to the LVOT in the presence of a deep implantation is associated with more frequent need for permanent pacing (28). We hypothesize that adjusted valve sizing algorithms that also take into account the LVOT dimensions may reduce the need for permanent pacemakers.

Part II – Vascular complications

TAVI requires large bore arterial access for the introduction of the valve delivery systems. Sheath sizes range from 14 to 20 French (5-7 mm). Arteriotomy closure most often requires percutaneous suture based devices. In the early TAVI experience major vascular complications occurred in approximately 12% of patients (29), of which two-thirds were due to failed arteriotomy closure (30). Despite rigorous improvements of TAVI over the past decade - including growing experience, improved access techniques, and smaller profiled devices - major vascular complications remain high (6,7). Chapter 6 and 7 describe the MANTA closure device, a novel collagen plug-based system (31,32). The Manta technology is intuitive, precludes technically demanding pre-closure with sutures and provides almost immediate hemostasis. Chapter 8 describes the multi-center CE mark trial with the Manta device including 50 patients from 9 centers who required large-bore vascular access closure (33). There was only one major vascular complication and hemostasis was rapid and reliable. Ultrasound follow-up confirmed arterial vessel patency up to 60 days after closure. Randomized trials comparing the MANTA with suture-based closure devices will have to confirm whether collagen-based technology yields better outcomes.

Part III – Neurological events

Neurological events may complicate TAVI including disabling stroke affecting independent living and impairing quality of life. The first randomized controlled trials with TAVI demonstrated an early penalty of major stroke at 30 days in 5% of patients versus 1.1% with conservative management (i.e. medical therapy and balloon aortic valvuloplasty) (3). Early head-to-head studies showed comparable stroke rates for TAVI versus SAVR (3.8 vs. 2.1% with Edwards Sapien and 4.9 vs. 6.2% with Corevalve) (4,5). Despite device iteration, procedural refinements and growing experience the overall stroke rate stagnated as was shown in recent trials including intermediate risk populations (TAVI 3.2% vs. SAVR 4.3%) (6).

Clinically overt strokes and transient ischemic attacks represent but the tip of the iceberg. Subtle changes in neurocognitive performance are often missed by genuine physical examination (34-36). Indeed, brain injury may occur in up to 93% of patients following TAVI (37) . Silent infarcts may not be trivial as they are associated with cognitive and functional decline and increased risk for stroke (38). As the focus of TAVI is moving to lower risk patients who are younger and have a longer life expectancy the relevance of these subclinical brain lesions may only increase.

More than half of the early strokes after TAVI occur within 48 hours of the procedure (12,39,40) and have a trombo-embolic origin (39,41). Histopathology studies of debris captured by filters in the major extracranial cerebral arteries during TAVI have undisputedly established the presence of cerebral embolization of thrombotic material and tissue derived debris during TAVI in nearly all patients (13). This finding paved a clear path for cerebral protection during TAVI. Chapter 9 provides a comprehensive overview of currently available embolic protection devices and the results from clinical studies (42). Although the concept of embolic protection seems sound, compelling clinical benefit is lacking (43-45). All randomized controlled trials relied on surrogate endpoints involving the occurrence of new brain injury by MRI assessment. Unfortunately, power calculation fell short and the trials suffered from a high drop-out rate in terms of the follow up brain imaging. Chapter 10 discusses the Erasmus MC driven multi-center randomized MISTRAL C trial on the effects of filter-based embolic protection system (46). Debris was caught in all patients who underwent TAVI, and the filters resulted in fewer and smaller brain lesions and preserved neurocognitive function. The current generation filter based embolic protection is limited by covering only three of the four cerebral vascular contributors leaving the left vertebral artery unprotected as was indicated by the absence of any effect in the posterior brain lobes. Of note, approximately a quarter of new brain lesions seem to be located in the cerebellum and brainstem which are largely vascularized by the left vertebral artery (47).

We expanded our research with a feasibility study including selective filter protection of the left vertebral artery to confirm for the first time the embolization of debris towards the left vertebral territory during TAVI (Chapter 11) (48). Future studies are warranted to evaluate the outcome of complete cerebral embolic protection. The challenge will be to define proper surrogate endpoints (e.g. lesions on brain-MRI, neurocognitive performance) and sufficient power as was proposed by a recent academic research consortium consensus document (49).

In Chapter 12 we explain that cerebral embolization of thrombotic and tissue related material is inherent to left sided structural heart interventions as it also occurred with catheter-based mitral intervention (50).

Part IV – Technical considerations

TAVI implies a complex interplay between the transcatheter heart valve stented frame within the aortic root. Part IV of this thesis zooms in on the technical considerations to optimize transcatheter valve implantation.

An optimal landing zone for a transcatheter heart valve would be a circular shaped tube slightly narrower than the intended prosthesis size to achieve a stabile position with adequate sealing. In reality a stenotic aortic valve represents an asymmetric more elliptic landing zone with an irregular surface. Incomplete sealing will result in paravalvular leaks during the diastolic phase. Significant paravalvular leaks are associated with premature mortality and should be avoided whenever possible (51,52).

Sealing fabric, repositioning features, metallic properties introducing adequate radial force and balloon postdilatation may help prevent paravalvular leaks but sometimes at the expense of conduction disorders or even fatal complications such as annular or LVOT rupture or aortic dissection.

Chapter 15 demonstrates a cohort with a diverging pallet of aortic root calcium distribution and subsequent stent frame eccentricity of the CoreValve transcatheter heart valve (53). Up to one third of the implanted bioprosthesis had an eccentric shaped stent frame which correlated with the amount of calcification and was associated with more paravalvular leak.

TAVI is now increasingly performed under local anesthesia. As a consequence, TAVI relies merely on contrast aortography to evaluate adequate positioning and paravalvular leaks and transesophageal echocardiography is fading out of every day procedural workflow. Chapter 16 demonstrates the importance of contrast aortography with TAVI using a repositionable and fully-retrievable mechanically expanded transcatheter heart valve. The data show a strong relation between implantation depth of the stented frame below the aortic annulus and subsequent need for a permanent pacemaker. Furthermore sealing of the bioprosthesis appeared irrespective of the implantation depth. Also, contrast aortography correlated satisfactorily with transthoracic echocardiography in terms of aortic regurgitation assessment.

Part V – Future perspectives

Degenerative aortic stenosis and left ventricular systolic dysfunction increase ventricular afterload, are more frequent in the elderly and often coexist. Afterload reducing agents such as beta-blockers and renin-angiotensin-aldosterone system modulators are the cornerstone of pharmacological management for patients with symptomatic heart failure. Aortic valve replacement to resolve an aortic stenosis reduces the left ventricular afterload. Current guidelines recommend careful monitoring for moderate aortic stenosis (16,17). The fate of moderate aortic stenosis in patients with LV systolic dysfunction is unknown. Conceivably, moderate aortic stenosis will affect the overall loading of the left ventricle as illustrated by the valvulo-arterial impedance (54). We found significant prognostic implications of moderate aortic stenosis in patients with impaired left ventricular systolic function (Chapter 17) (55). The rate of death, aortic valve replacement or hospitalization for heart failure exceeded 60% at 4 years of follow-up. Male sex, higher transaortic velocities and symptomatic heart failure were important predictors of events. Most clinical events occurred during the first year after diagnosis. Early TAVI might improve the overall prognosis and quality of life and is the subject of an ongoing randomized trial (56).

Bicuspid aortic valve stenosis has so far been excluded from randomized TAVI trials. Several international collectives reported acceptable clinical outcomes with TAVI as an off-label treatment for severe bicuspid AS (57). Initial experience was hampered by a high rate of at least moderate paravalvular leaks. A recent report suggested that the incidence of significant PVL might be less with new-generation transcatheter heart valves as compared to the earlier generations (58).

Chapter 18 reports post-market study data of clinical and echocardiographic outcomes of TAVI with the mechanically expanded Lotus valve in patients with bicuspid aortic valve stenosis as compared to patients with tricuspid aortic valve stenosis. Both the clinical outcome and the rate of more than trivial PVL were comparable between the two entities, in contrast to studies with earlier generation valves (57,59).

Conclusion and future directions

This thesis contemplates current challenges of TAVI and focuses on three important entities. Conduction disorders remain a frequent issue. Daily ECG analysis after the procedure may help predict the fate of acquired conduction abnormalities at an earlier stage and identify the patients who would benefit from (early) permanent pacemaker implantation.

Access site management relies on suture-based techniques and has inherent limitations. Collagen plug based closure is a different mechanism, may be easier to adopt and globally reduce vascular complications.

Brain injury seems omnipresent after TAVI and is difficult to reconcile with the "primum non nocere" principle. Filter based embolic protection hold promise to mitigate the effects of cerebral embolization, especially if complete protection is achieved.

TAVI has now matured into a simplified procedure under local anesthesia and the performance of the latest transcatheter valve iterations approach or even supersede what can be achieved with a surgical bioprosthesis. Bicuspid aortic disease, severe aortic regurgitation and moderate AS in heart failure are potential new indications for TAVI. Furthermore, TAVI is attractive for treatment in patients at lower risk who are younger and have a longer life expectancy.

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Nederlandse samenvatting

Degeneratieve aortaklepstenose is een progressieve aandoening met een piek in de oudere populatie. Hoewel voorheen chirurgische aortaklepvervanging door middel van een open-hart operatie de standaard behandeling voor deze patiënten was, is dit landschap aan het veranderen. Vijftien jaar geleden voerde professor Alain Cribier voor het eerst een minder invasieve behandeling voor deze aandoening uit, de kathetergebonden aortaklepimplantatie (transcatheter aortic valve implantation - TAVI). Initieel werd deze methode uitgevoerd bij patiënten die inoperabel werden beschouwd of waarbij het risico op het optreden van overlijden of ernstige complicaties bij een chirurgische aortaklepvervanging te hoog werd ingeschat, maar inmiddels is TAVI uitgegroeid tot de hoeksteen van de behandeling. Terwijl de techniek van TAVI steeds verder wordt verfijnd, verschuift de toepassing van TAVI naar patiënten met een intermediair operatierisico. Het besluit om een chirurgische aortaklepvervanging of een TAVI uit te voeren bij een individuele patiënt vindt plaats in een multidiscplinair hartteam, bestaande uit thoraxchirurgen, interventiecardiologen, beeldvormingscardiologen, geriaters en anesthesisten. Hoewel het concept van TAVI tot de verbeelding spreekt en ogenschijnlijk minder invasief zou zijn dan chirurgische aortaklepvervanging worden bij deze methode nog altijd complicaties gezien. In dit proefschrift zal in eerste instantie in worden gegaan op de belangrijkste complicaties die rondom TAVI optreden en worden mogelijke oplossingen tegen het licht gehouden om zodoende de procedure te verfijnen. In tweede instantie zal dit proefschrift zich richten op de toepassing van TAVI voor andere indicaties dan louter ernstige degeneratieve aortaklepstenose.

Het ontwerp van kathetergebonden klepsystemen wordt door fabrikanten continu verfijnd ten behoeve van de werkzaamheid en veiligheid van TAVI. Over de laatste jaren is hierdoor een veelvoud aan klepsystemen beschikbaar gekomen waardoor artsen in staat zijn om de behandeling af te stemmen op individuele patiënten. Tegelijkertijd wordt de procedure eenvoudiger te hanteren en wordt het ziekenhuisopname rondom de ingreep verkort waardoor scenario's zich aandienen waarbij de patiënt op dezelfde dag van de procedure nog het ziekenhuis verlaat.

Een essentieel onderdeel van de ingreep is beeldvorming voorafgaand aan de procedure om zodoende de juiste behandeling en klepsysteem voor de patiënt te kiezen. Voornamelijk 'multi-slice computed tomography' (MSCT) van de arteriële vaatboom en aortaklep omvatten cruciale informatie. Hoofdstuk 1 omvat een beschrijving van de huidige generatie klepsystemen en methoden om de juiste klepmaat en type te selecteren.

De Lotus klep is momenteel het enige klepsysteem waarbij implantatie plaatsvindt door mechanische expansie. Ook is Lotus het enige systeem waarbij de klep in zijn volledigheid gerepositioneerd en zelfs uit de patiënt kan worden teruggetrokken. Deze unieke eigenschappen maken dat dit klepsysteem de voorkeur geniet boven andere klepsystemen wanneer het gaat om complexe anatomie waarbij onzekerheid bestaat over de klepdimensies of bij ernstige verkalking van de aortawortel. Hoofdstuk 2 omvat een gedetailleerde omschrijving van het concept van de Lotus klep en geeft een stapsgewijze beschrijving van de implantatie.

De eerste resultaten van nieuwe generatie klepsystemen zijn veelbelovend. Vanzelfsprekend hebben de uiteenlopende specificaties hiervan zowel voor- als nadelen, welke uitvoerig worden besproken in dit proefschrift.

Deel I – Geleidingsstoornissen

Net als met chirurgische aortaklepvervanging is TAVI geassocieerd met het optreden van nieuwe, alsmede toename van bestaande geleidingsstoornissen van het hart. Dit kan ertoe leiden dat patiënten afhankelijk worden van een pacemaker.

Anatomisch gezien is de plek waar de klepprothese wordt geïmplanteerd, namelijk tussen de aortaklep annulus en de linker ventrikel uitstroombaan, dicht gelegen bij het elektrische geleidingssysteem van het hart. Voldoende radiaire expansie is een voorwaarde voor een stabiele kleppositie en functionaliteit van de klepprothese. Dientengevolge wordt radiaire kracht op het geleidingssysteem uitgeoefend en kan schade optreden. De implicaties van deze nieuw ontstane geleidingsstoornissen vormen de basis van geraffineerd onderzoek.

Het is belangrijk om te realiseren dat de meeste nieuwe geleidingsstoornissen reeds ontstaan bij minimaal contact met de linker ventrikel uitstroombaan door bijvoorbeeld voerdraden of katheters en waarbij de klepprothese dus nog niet daadwerkelijk geïmplanteerd is. De meerderheid van deze nieuwe geleidingstoornissen zijn tijdelijk van aard, maar sommigen zijn permanent of nemen zelfs toe nadat de procedure voltooid is. De betekenis van deze nieuwe geleidingsstoornissen zijn nog niet volledig opgehelderd, maar deze zouden waardevolle informatie kunnen bevatten om de veiligheid van de patiënt in te schatten en hierop ziekenhuisrichtlijnen aan te passen.

De verfijning van TAVI heeft ertoe geleid dat patiënten steeds sneller na de procedure naar huis worden ontslagen. Het optreden van geleidingstoornissen na TAVI vormen hiervoor een belangrijke hindernis. In Hoofdstuk 3 onderzoeken wij of de interventriculaire geleidingstijd (i.e. de QRS-duur op het ECG) een waardevolle voorspeller zou kunnen zijn voor het optreden van permanente hooggradige geleidingsstoornissen met uiteindelijk noodzaak voor een pacemaker. Het betreft een retrospectieve analyse van dagelijks verkregen ECG's van patiënten na TAVI. Wij stelden vast dat patiënten met een stabiele korte QRS-duur ook voorbijgaande hooggradige geleidingsstoornissen kunnen ontwikkelen, maar dat deze nagenoeg altijd tijdens opname herstelden en dat zij dus uiteindelijk geen pacemaker nodig zullen hebben. Daarentegen hadden patiënten met een persisterend verlengde QRS-duur een hoog risico op het ontwikkelen van hooggradige geleidingsstoornissen en dus noodzaak voor een pacemaker. Het dagelijks verkrijgen van een ECG hielp ons om patiënten te identificeren waarbij het geleidingssysteem herstelde en dus vroeg uit het ziekenhuis konden worden ontslagen. Deze bevinding zal nog in een groter prospectief cohort gevalideerd moeten worden.

Een rechter bundeltakblok komt bij ~20% van de patiënten die een TAVI procedure moeten ondergaan voor, en zij zijn hiermee bij uitstek kwetsbaar voor hooggradige geleidingsstoornissen en noodzaak voor een pacemaker. In Hoofdstuk 4 bestuderen wij of het selecteren van een bepaald klepsysteem kan bijdragen om de noodzaak voor een pacemaker te omzeilen. Hoewel bij deze patiënten met pre-existent rechter bundeltakblok alle klepsystemen geassocieerd waren met een hogere kans op noodzaak voor een pacemaker, was dit risico het hoogst met de Lotus klep. Deze bevinding benadrukt dat het samenspel tussen het type klepsysteem en een reeds aangetast geleidingssysteem in overweging genomen moet worden voordat een bepaald klepsysteem gekozen wordt.

Klepprothesen zijn afhankelijk van radiaire expansie om zich te verankeren in de aortawortel. De huidige maatselectie voor klepprothesen richt zich op de dimensies van de aortaklep annulus. Echter, het geleid-

ingssysteem ligt enkele millimeters onder de annulus het meest aan de oppervlakte, in de linker ventrikel uitstroombaan (LVOT). De LVOT is doorgaans nauwer dan de aorta annulus. De consequentie is dat als de maatselectie berust op de annulus er behoorlijke 'oversizing' plaatsvindt ter hoogte van de LVOT. Hoofdstuk 5 bevestigd dat 'oversizing' ter hoogte van de LVOT in combinatie met een diepere implantatie geassocieerd is met frequentere noodzaak voor een pacemaker. Wij suggereren hiermee dat aangepaste maatselectie (waarbij rekening gehouden wordt met de dimensies van de LVOT) zou kunnen bijdragen aan het reduceren van het aantal benodigde pacemakers.

Deel II – Vasculaire complicaties

TAVI vereist een grote arteriële (slagaderlijke) toegang voor het introduceren van het klepsysteem. De sheathgrootte varieert hierbij van 14 tot 20 French (5-7 mm). Het sluiten van de arteriële toegang wordt over het algemeen verricht door middel van systemen waarmee een hechting op de bloedvatwand kan worden geplaatst, zogenoemde 'suture-based' systemen. Tijdens de initiële ervaringen met TAVI werden bij 12% van de patiënten majeure vasculaire complicaties gezien, waarvan twee-derde het gevolg waren van een niet-succesvolle sluiting van de arteriële toegang. Ondanks significante verbeteringen van TAVI in de afgelopen 10 jaar – waaronder groeiende ervaring, verbeterde methodes voor het verkrijgen van arteriële toegang en klepsystemen met kleinere profielen – blijft de incidentie van majeure vasculaire complicaties hoog.

Hoofdstuk 6 en 7 beschrijven MANTA, een vernieuwend systeem waarbij de arteriële toegang wordt gesloten met een collageen-plug ('collagen-based' sluiting). De MANTA technologie is intuïtief, vereist geen technisch uitdagende sluiting voorafgaand aan de index-procedure, en zorgt voor bijna directe hemostase. Hoofdstuk 8 beschrijft de multi-center CE-markering trial met het MANTA systeem met 50 patiënten uit 9 verschillende centra bij wie het sluiten van grote arteriële toegang noodzakelijk was. Er was slechts één majeure vasculaire complicatie en de hemostase was doorgaans vlot en betrouwbaar. Controle-echo bevestigde een intacte arterie tot op 60 dagen na sluiting. Gerandomiseerde studies waarbij MANTA wordt vergeleken met 'suture-based' systemen zullen moeten gaan aantonen of 'collagen-based' systemen ook hun weerslag hebben op belangrijke klinische uitkomstmaten.

Deel III – Neurologische complicaties

Na TAVI treden soms neurologische complicaties op, zoals een invaliderende beroerte, met vanzelfsprekend veel impact op de zelfstandigheid en kwaliteit van leven. Bij de eerste gerandomiseerde trials met TAVI werden 5% majeure beroertes gezien op 30 dagen na de TAVI procedure, tegenover 1.1% bij de patiënten die conservatief werden behandeld (medicamenteus en ballon-valvuloplastiek).

De eerste studies die TAVI vergeleken met chirurgische aortaklepvervanging toonden vergelijkbare incidenties van beroerte (respectievelijk 3.8% vs. 2.1% met Edwards Sapien en 4.9% vs. 6.2% met CoreValve). Ondanks verbeterde klepsystemen, verfijning van de procedure en groeiende ervaring is de incidentie van beroertes gestagneerd, wat onlangs nog werd bevestigd in patiëntenpopulaties met een intermediair operatierisico (TAVI 3.2% vs. chirurgische aortaklepvervanging 4.3%).

Klinisch waarneembare beroertes en 'transient ischemic attacks' (TIA's) vormen slechts de top van de ijsberg. Subtiele veranderingen in neurologisch functioneren worden doorgaans gemist bij een standaard lichamelijk onderzoek. Inderdaad treed bij tot 93% van de patiënten na TAVI op MRI waarneembare schade aan het brein op. Deze 'stille' infarcten zijn mogelijk niet irrelevant, aangezien zij geassocieerd zijn met cognitieve en functionele achteruitgang en bovendien een verhoogd risico geven op een beroerte in de toekomst. Aangezien de focus van TAVI zich verplaatst naar patiënten met een lager operatierisico en een langere levensverwachting zal de relevantie van deze subklinische hersenschade vermoedelijk alleen maar toenemen.

Meer dan de helft van de vroeg optredende beroertes na TAVI treden binnen 48 uur na de procedure op, en zijn trombo-embolisch van aard. Histopathologisch onderzoek van het debris dat tijdens TAVI werd opgevangen in de grote hersenbloedvaten heeft aangetoond dat embolizatie van trombotisch materiaal naar het brein bij nagenoeg alle procedures voorkomt. Deze bevinding maakte vrij baan voor cerebrale protectie tijdens TAVI. Hoofdstuk 9 omvat een uitgebreid overzicht van de huidig beschikbare cerebrale protectiesystemen en de resultaten hiervan uit klinische onderzoeken.

Hoewel het concept van cerebrale protectie zeer uitnodigend is, blijven overtuigende klinische resultaten vooralsnog uit. Gerandomiseerde studies naar TAVI met en zonder cerebrale protectie richtten zich op surrogate eindpunten zoals het optreden van nieuwe laesies op MRI. Helaas werden te weinig patiënten in deze studie geïncludeerd om een effect aan te tonen en bovendien verschenen veel patiënten niet voor de vervolgonderzoeken na TAVI. Hoofdstuk 10 bediscussieert de door het Erasmus MC gedreven gerandomiseerde multi-center MISTRAL C trial waarin de effecten van 'filter-based' cerebrale protectie werden onderzocht. Bij alle patiënten die TAVI ondergingen werd in filters in de grote hersenbloedvaten debris opgevangen. Het gebruik van de filters resulteerde in minder en kleinere laesies op de MRI scan na TAVI en tevens behouden neurocognitieve functies. De huidige generatie 'filter-based' cerebrale protectie beschermt slechts drie van de vier grote hersenbloedvaten, waarbij de linker arteria vertebralis onbeschermd blijft, wat teruggezien werd in het uitblijven van een beschermend effect in de achterste hersenkwabben. Dit sluit aan bij eerdere studies waarbij een kwart van de nieuwe breinlaesies (bij patiënten zonder cerebrale protectie) gelokaliseerd was in het cerebellum en de hersenstam, waarvan de linker arteria vertebralis een belangrijk aanvoerend bloedvat is.

Wij breidden ons onderzoek uit door de linker arteria vertebralis selectief te beschermen, waarmee voor het eerst werd bevestigd dat debris ook via deze route emboliseert tijdens TAVI (Hoofstuk 11). Toekomstige studies zijn noodzakelijk om te evalueren of complete cerebrale protectie daadwerkelijk betere klinische uitkomsten oplevert. Een belangrijke uitdaging ligt in het juist definiëren van surrogate eindpunten (bijv. laesies op cerebrale MRI, neurocognitief functioneren) en het includeren van voldoende patiënten. Er is onlangs een consensus document opgesteld waarin dit duidelijk staat gedefinieerd.

In Hoofstuk 12 benadrukken wij dat cerebrale embolizatie van trombotisch- en weefselmateriaal inherent is aan alle linkszijdige structurele interventies aan het hart, aangezien het ook voorkomt bij katheter-gebonden interventies aan de mitralisklep.

Deel IV – Technische overwegingen

TAVI omvat een complex samenspel tussen het stentframe van de klepprothese en de aortawortel. Deel IV van dit proefschrift zoomt in op technische overwegingen om de klepimplantatie te optimaliseren.

Een optimale landingszone voor een klepprothese zou een circulaire buis zijn, met een iets nauwere diameter dan de beoogde maat van de klepprothese zodat een stabiele positie met adequate afdichting rondom de klepprothese wordt verkregen. In de realiteit is een stenotische aortaklep een asymmetrische elliptische landingszone met een irregulair oppervlak. Inadequate afdichting rondom de klepprothese resulteert in paravalvulaire lekkage tijdens de diastolische fase. Significante paravalvulaire lekkage is geassocieerd met vroegtijdig overlijden en moet daarom voorkomen worden voor zover mogelijk.

Materiaal rondom de klepprothese voor optimale afdichting, mogelijkheid tot repositioneren, eigenschappen van het stentmateriaal met adequate radiaire kracht en ballon postdilatatie kunnen bijdragen aan het voorkomen van paravalvulaire lekkage. Echter gaan deze eigenschappen soms ten koste van het optreden van geleidingsstoornissen of zelfs fatale complicaties zoals annulus of LVOT ruptuur of aortadissectie.

Hoofdstuk 15 toont een cohort patiënten met uiteenlopende mate van verkalking van de aortawortel en dientengevolge een excentrisch stentframe na implantatie van de CoreValve klepprothese. Tot een-derde van de geïmplanteerde klepprothesen hadden een excentrisch gevormd stentframe, wat correleerde met de hoeveelheid calcificatie en op zijn beurt met meer paravalvulaire lekkage.

TAVI wordt in toenemende mate toegepast onder lokale verdoving. Hierdoor is TAVI steeds meer afhankelijk van angiografie om de positie en paravalvulaire lekkage te beoordelen en wordt transoesophageale echocardiografie (slokdarmecho) tijdens de procedure nog zelden gebruikt. Hoofdstuk 16 toont het belang van angiografie tijdens TAVI met een repositioneerbare en volledig uitneembare mechanisch geëxpandeerde klepprothese. De resultaten tonen een sterke relatie tussen de implantatiediepte van het stentframe onder de aorta-annulus enerzijds en de noodzaak voor een pacemaker anderzijds. Bovendien bleek de afdichting rondom de klepprothese adequaat ongeacht de implantatiediepte. Ook was de beoordeling van paravalvulaire lekkage op angiografie en transthoracale echocardiografie sterk gecorreleerd.

Deel V – Toekomstperspectief

Degeneratieve aortaklepstenose en verminderde systolische linker ventrikel functie verhogen de afterload van het hart. Beide aandoeningen komen vaker voor bij ouderen en bestaan vaak ook tegelijkertijd. Afterload verlagende medicatie zoals betablokkers en medicijnen die aangrijpen op het renine-angiotensine-aldosteron-systeem vormen de hoeksteen van de medicamenteuze behandeling van patiënten met symptomatisch hartfalen. Aortaklepvervanging bij patiënten met een ernstige aortaklepstenose is ook een methode om de linker ventrikel afterload te verlagen. Bij patiënten met een voorstadium hiervan waarbij de stenose nog matig is adviseren de huidige richtlijnen om deze patiënten zorgvuldig te monitoren. De implicaties van een matige aortaklepstenose in het bijzijn van een verminderde systolische linker ventrikel functie zijn nog onbekend. Het is aannemelijk dat een matige aortaklepstenose zijn weerslag heeft op de algehele belasting van de linker ventrikel zoals geïllustreerd wordt door de valvulo-arteriële impedantie. Wij toonden belangrijke prognostische implicaties aan van een matige aortak-

lepstenose bij patiënten met een verminderde systolische linker ventrikel functie (Hoofdstuk 17). Het gecombineerde eindpunt - dood, aortaklepvervanging of ziekenhuisopname voor hartfalen - trad op bij meer dan 60% van de patiënten na 4 jaar follow-up. Belangrijke voorspellers voor het optreden van het eindpunt waren: mannelijk geslacht, hogere gradiënten over de aortaklep en symptomatisch hartfalen. De meeste klinische eindpunten traden op binnen een jaar na het vaststellen van de diagnose. Vroegtijdige behandeling met TAVI zou de algehele prognose en kwaliteit van leven van deze patiënten kunnen verbeteren, en dit wordt momenteel onderzocht in een gerandomiseerde studie.

De aortaklep bestaat gewoonlijk uit drie klepbladen (tricuspide). Aortastenose is een degeneratieve ziekte die gekarakteriseerd word door valvulaire endotheelschade, inflammatie en calcificatie. Degeneratie van de aortaklep ontwikkeld zich over vele jaren en komt vaak pas op oudere leeftijd aan het licht. In 2 tot 5 procent van de algehele bevolking heeft de aortaklep in aanleg slechts twee klepbladen (bicuspide). Bicuspide kleppen zijn kwetsbaarder voor degeneratieve aortaklepstenose en hierdoor presenteren patiënten hierbij zich vaak op jongere leeftijd met symptomen. TAVI is mogelijk uitdagender bij patiënten met een bicuspide aortaklepstenose. Patiënten met een bicuspide aortaklepstenose werden geëxcludeerd voor de grote gerandomiseerde TAVI trials. Enkele internationale collectieven rapporteerden acceptabele klinische uitkomsten met TAVI als een off-label behandeling voor ernstige bicuspide aortaklepstenose. De eerste klinische ervaringen werden belemmerd door frequent optreden van ten minste matige paravalvulaire lekkage. Een recentere studie suggereerde dat de incidentie van significante paravalvulaire lekkage minder zou zijn met de nieuwe-generatie klepsystemen in vergelijking met de eerdere generaties.

Hoofdstuk 18 toont de resultaten uit een post-market studie welke zich richtte op de klinische en echocardiografische uitkomsten van TAVI met de mechanisch geëxpandeerde Lotus klep bij patiënten met een bicuspide aortaklepstenose tegenover patiënten met een tricuspide aortaklepstenose. Zowel de klinische uitkomsten als het optreden van belangrijke paravalvulaire lekkage waren vergelijkbaar tussen de twee entiteiten, in tegenstelling tot studies met eerdere generatie klepsystemen.

Conclusie en nieuwe uitdagingen

Dit proefschrift overdenkt de huidige uitdagingen van TAVI en focust op drie belangrijke entiteiten. Geleidingsstoornissen blijven een belangrijk probleem. Analyse van dagelijks verkregen ECG's na de procedure kan een vroege voorspelling doen over de uiteindelijke gevolgen van nieuw ontstane geleidingsstoornissen zodat patiënten die baat hebben bij een (vroege) pacemaker implantatie geïdentificeerd kunnen worden.

Het sluiten van de arteriële toegang voor TAVI wordt nog hoofdzakelijk verricht met behulp van 'suture-based' methoden, maar deze hebben belangrijke beperkingen. Collageen 'plug-based' sluiting past een andere techniek toe. Deze methode zou makkelijker toe te passen zijn en het zou vasculaire complicaties kunnen terugdringen.

Cerebrale schade lijkt onvermijdelijk na TAVI en is moeilijk te rijmen met het "primum non nocere" ("als eerste zult gij niet schaden") principe. 'Filter based' cerebrale protectie is een veelbelovende methode om cerebrale embolizatie te voorkomen, vooral als volledige protectie kan worden bereikt.

TAVI is uitgegroeid tot een gesimplificeerde procedure die onder lokale verdoving plaats kan vinden en de

werkzaamheid van de huidige klepsystemen benadert of overstijgt zelfs de chirurgische klepvervanging. Bicuspide aortaklepziekte, ernstige aorta insufficiëntie en matige aortaklepstenose in combinatie met hartfalen zijn potentieel nieuwe indicaties voor TAVI. Bovendien vormt TAVI een aantrekkelijke behandeling voor patiënten met een lager operatierisico welke doorgaans jonger zijn en een langere levensverwachting hebben.

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2009. We hebben aan interessante projecten over percutane coronaire interventies gewerkt. Ik besefte al snel dat onderzoek binnen de cardiologie een wervelend gebied is, waar ik deel van wilde blijven uitmaken. Ik ontmoette interessante mensen op het trial-bureau waarmee ik later opnieuw mocht samenwerken, waaronder Nico, Arno, Mattie, Ron en Eric. Ik ontmoette in die periode ook Sanne en Laura, bedankt voor jullie motiverende woorden en oprechte betrokkenheid door de jaren. Mattie, bedankt dat jij mij aan Nicolas hebt voorgesteld, jij hebt deze cascade in gang gezet. Eric, bedankt voor jouw altijd bruikbare feedback en lessen in de statistiek.

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Andrey, we had an intense collaboration throughout my PhD. The limitless enthusiasm that you put into the meetings that we had, was inspiring. In the meantime your carreer took another course. I wish you the best of luck my friend.

Rutger-Jan en Robert, julllie hebben als promovendi onder leiding van prof. De Jaegere al prachtige resultaten geboekt. De toon was hiermee gezet. Het is leuk om jullie voetsporen nog overal tegen te komen. Herbert, Nahid en Zouhair. Het is goed om te zien dat talentvolle onderzoekers de uitgezette lijnen voortzetten en ook met mooie nieuwe ideeën komen. Ik hoop naast mijn klinische werk ook nog een belangrijke bijdrage te mogen leveren aan jullie onderzoek. Ik had het geluk om tijdens mijn promotieonderzoek samen te mogen werken met toegewijde geneeskundestudenten die voor het eerst kennismaakten met wetenschappelijk onderzoek. Casper, Leonoor en Yaar, dank voor jullie bijdrage aan dit geheel. Ik twijfel niet dat jullie een glansrijke carrière te wachten staat, of dit nu binnen de cardiologie of een ander specialisme zal zijn.

Bob, bedankt dat ik jouw creatieve geest heb mogen gebruiken voor het ontwerpen van mijn cover. Jij blijft mij verbazen.

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Ba-302 was een kamer met mensen uit vele uithoeken van de wereld. Om te beginnen, Rene (uit Spike

city), jij bent een onmisbare spin in het web van de functieafdeling. Als er iets loos is dan fix jij het. Hannah (uit Oostvoorne), wij bespraken alle dagelijkse strubbelingen van het onderzoek. Wij hebben van onze promotietijd een gezellige tijd gemaakt. Jackie (from Schotland), you are such a wonderful person. I have seldom met someone so dedicated. You are a specialist although you don't always take the credit for it. You are an inspiration to your colleagues. Let's talk again over a glass of scotch! Claire (from Chendu, China), we had so much fun. Your talent to make high quality echo's doesn't stop to amaze me. You became more and more a key player in the valve programme. Mihai (from Romenia), you completed the Ba-302 crew. You taught me a lot about echo's and I like your way of doing research, complete and accurate. I am looking forward to your dissertation as well. Marcel, jij was ongeveer net zo vaak op onze kamer als elders in het ziekenhuis. Als jij binnen kwam lopen wist men al dat er een goede grap of interessante discussie op gang ging komen. Dank voor de leuke samenwerking in het Erasmus MC en in het voetbalveld.

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Het maatschap cardiologie in Breda, bedankt voor de leuke samenwerking tijdens mijn eerste stappen in de kliniek. In het bijzonder Marco, dank voor jouw vertrouwen en positieve feedback. Rohit, dank voor jouw heldere input toen er belangrijke beslissingen genomen moesten worden. Claudia, onze carrières lopen sinds onze ontmoeting in Breda parallel. Ik hoop dat wij dit zij-aan-zij voortzetten.

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voegen wij er daar nog veel aan toe. Gijs. met jou heb ik één van de mooiste periodes van mijn leven beleefd in Zuid-Afrika. Bedankt voor jouw vriendschap en humor. Ik twijfel niet dat jij ook bij de anesthesie een pit zult spelen. Els en Michael, jullie zijn altijd leuk gezelschap, zowel in 'de Kuip' als erbuiten. Jullie vrolijke vibe is altijd een opsteker voor mij, bedankt!

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PhD Portfolio

Research activities

	Year	Workload (ECTS)
General academic and research skills		
NIHES - Diagnostic research	2015	0.8
NIHES - Biostatistics for clinicians	2015	1.3
NIHES - Regression analysis	2015	1.6
Rules and organization of clinical research (BROK) course	2015	1.5
Good-clinical practice (GCP) course	2015	0.3
Scientific integrity	2015	0.3
English writing course	2016	3.0
NIHES - Prediction modelling course	2016	0.9
In-depth courses		
COEUR - Arterial thrombosis in acute ischemic stroke	2014	0.2
COEUR - Vascular epidemiology	2014	1.5
COEUR - Diagnostic Imaging	2014	1.5
COEUR - Cost, quality and value in cardiovascular interventions	2015	0.3
COEUR day	2015	0.4
Conferences and symposia		
NVVC conference	2015	0.9
EuroPCR conference	2015	4.8
ESC conference	2015	4.8
London valves conference	2015	3.6
NVVC conference	2015	0.9
CRT meeting	2016	1.2
ACC conference	2016	1.2
NVVC conference	2016	0.9
EuroPCR conference	2016	4.8
DRES summit	2016	0.9
Supervising practicals and Master theses		
Supervising writing a systematic review of 2nd year medical students	2015-2016	0.6
Supervising research of 2nd year medical students	2015-2016	0.9
Supervising research of 4th year medical student	2015-2016	0.3
Lectures for technical university students	2016	0.6
Total		*40*

Presentations

		No. of presentations
Oral presentations		
Dutch society of cardiology (NVVC) Spring conference, Noordwijkerhout, The Netherlands	2015	1
EuroPCR conference, Paris, France	2015	2
European society of cardiology (ESC) conference, London, United Kingdom	2015	1
London valves conference, Berlin, Germany	2015	2
Dutch society of cardiology (NVVC) Autumn conference, Noordwijkerhout, The Netherlands	2015	1
Dutch society of cardiology (NVVC) Spring conference, Noordwijkerhout, The Netherlands	2016	1
EuroPCR conference, Paris, France	2016	3
Dutch revascularization and electrophysiology summit (DRES), Nijkerk, The Netherlands	2016	1
London valves conference, London, United Kingdom	2016	1
Poster presentations		
Trancatheter cardiovascular therapeutics (TCT) conference, San Francisco, United States of America	2015	1
Cardiovascular research technologies (CRT) conference, Washington DC, United States of America	2016	1
American college of cardiology (ACC) conference, San Francisco, United States of America	2016	1
Trancatheter cardiovascular therapeutics (TCT) conference, Denver, United States of America	2017	1
Total		*17*

List of publications

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7. van Gils L, Clavel MA, Vollema EM, Hahn RT, Spitzer E, Delgado V, Nazif T, De Jaegere PP, Geleijnse ML, Ben-Yehuda O, Bax JJ, Leon MB, Pibarot P, Van Mieghem NM. Prognostic Implications of Moderate Aortic Stenosis in Patients With Left Ventricular Systolic Dysfunction. Journal of the American College of Cardiology. 2017;69(19):2383-92.

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9. van Gils L, De Jaegere PP, Roubin G, Van Mieghem NM. The MANTA Vascular Closure Device: A Novel Device for Large-Bore Vessel Closure. JACC Cardiovascular interventions. 2016;9(11):1195-6.

10. van Gils L, Rodriguez Olivares R, Ren B, Geleijnse ML, Kappetein AP, De Jaegere PPT, Van Mieghem

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About the author

Lennart van Gils was born on the 28th of November 1989, in Gouda, The Netherlands. After graduating high school (Coenecoop College, Waddinxveen) he moved to Rotterdam to start medical school at the Erasmus University. During his studies he participated in research on percutaneous coronary interventions at the interventional cardiology department of the Erasmus Medical Center, supervised by dr. Sanneke de Boer and prof. dr. Eric Boersma. He did a clinical internship abroad in Cape Town, South Africa. After obtaining his Medical Doctor's degree in 2014, he started his research fellowship focusing on TAVI related complications, supervised by prof. dr. Peter P. De Jaegere and dr. Nicolas M. Van Mieghem. During this PhD project he had the opportunity to present his work at international conferences and to publish manuscripts in peer-reviewed journals. He was also involved in the clinical TAVI program by performing CT analyses and attending the institutions' heart team. In January 2017 he started working as a clinical resident at the cardiology department of the Amphia Hospital Breda and in October 2017 he continued his residency at the cardiology department of the Erasmus Medical Center.

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