Transapical Mitral Implantation of the Tiara Bioprosthesis

Pre-Clinical Results

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Objectives This study sought to describe the pre-clinical evaluation of transapical mitral implantation of the Tiara (Neovasc Inc, Vancouver, British Columbia, Canada) valve in preparation for first-in-man implantation.

Background The Tiara is a transcatheter self-expanding mitral bioprosthesis, specifically designed for the complex anatomic configuration of the mitral apparatus.

Methods Tiara valves were implanted in a short-term porcine model, in a long-term ovine model, and in human cadavers.

Results Short-term and long-term evaluation demonstrated excellent function and alignment of the valves, with no left ventricular outflow tract obstruction, coronary artery obstruction, or transvalvular gradients. Long-term evaluation of 7 sheep demonstrated clinically stable animals. A mild degree of prosthetic valve regurgitation was seen in 2 of the 7 sheep. A mild-to-moderate degree of paravalvular leak, which was attributed to this animal model, was observed in 6 of these animals. Cardioscopy and macroscopic evaluation demonstrated stable and secure positioning of the Tiara valve with no evidence of injury to the ventricular or atrial walls. Pericardial leaflets were free and mobile without calcifications. Implantation of the Tiara valves in human cadaver hearts demonstrated, upon visual inspection, proper anatomic alignment and seating of the valve, both at the atrial and at the ventricular aspects of the native mitral apparatus.

Conclusions In preparation for the first-in-man transcatheter mitral valve implantation, we report the successful pre-clinical evaluation of the Tiara transcatheter self-expanding mitral bioprosthetic valve. In porcine and ovine models without mitral regurgitation, transapical mitral implantation of the Tiara valve is technically feasible and safe, and results in a stable and well-functioning mitral bioprosthesis.

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Severe mitral regurgitation (MR) is commonly associated with dilation of the heart and advanced coronary artery disease, ultimately resulting in disability and death from congestive heart failure. Although surgery remains the gold standard treatment for MR, approximately one-third of potential candidates are considered to be at too high risk for surgical repair or replacement (1–3). Severe MR affects approximately 2% of the population, but its prevalence increases to 13.3% among patients 75 years of age or older in industrialized countries. With advances in medicine enhancing longer survival, the incidence of severe MR is expected to rise dramatically (4).

Various novel percutaneous transcatheter valvular technologies have emerged as alternatives to open surgery for high-risk patients (5). These technologies are classified according to the part of the heart that is being targeted: the leaflets—percutaneous leaflet plication, leaflet coaptation, or radio-frequency leaflet ablation; the annulus—indirect annuloplasty through the coronary sinus, or direct annuloplasty either true percutaneous or by a hybrid approach through the left atrium; the chordae—percutaneous chordal plication, or the left ventricle (LV)—percutaneous LV remodeling. The percutaneous edge-to-edge repair technology has been shown to be noninferior to open repair in randomized clinical trials. However, percutaneous mitral valve repair is not possible for many patients, and therefore, mitral valve (MV) replacement may be an attractive alternative (5,6). Several transcatheter MV implantation technologies, either transapical or transseptal, are in various stages of pre-clinical evaluation (7–9).

The Tiara (Neovasc Inc, Vancouver, British Columbia, Canada) is a catheter-based self-expanding mitral bioprosthesis, specifically designed to fit the complex anatomic structure of the mitral apparatus. It is implanted using a transapical approach. The valve assembly is shaped to match the natural orifice of the mitral valve and minimize obstruction of the LV outflow tract (10). We describe here the pre-clinical assessment of the Tiara valve in short-term and long-term animal models, as well as in human cadaver hearts, performed as part of the preparation for the planned first-in-man transapical mitral implantation (TAMI).

Methods

Valve properties. The Tiara bioprosthetic valve is fabricated using cross-linked bovine pericardial tissue leaflets mounted inside a self-expanding metal alloy frame and cramped onto a short, flexible 32-F delivery catheter for transapical delivery (Fig. 1). A retractable sheath retains the valve in place until deployment. The atrial portion engages the area of the left atrium surrounding the mitral annulus, and a series of anchoring structures actively engage the mitral leaflets and chordae within the LV, securing the valve from retrograde dislodgement during systole. During all stages of valve implantation until the final release and deployment, it is possible to recapture the partially deployed valve and retrieve it into the delivery catheter, reposition, and restart the implantation process. Tiara implantation, orientation, and alignment was performed under simultaneous echocardiographic and fluoroscopic guidance using a specific radiopaque set of markers on the nitinol frame and on the delivery system.

TAMI implantation protocols. The animal protocols were approved by the Montreal Heart Institute’s Animal Care and Use Committee, and the animal care and use committee of the Institute Mutualiste Montsouris Recherche, Paris, France. The protocol for human cadaver trials was approved by the Seattle Science Foundation, Seattle, Washington.

Transapical implantation of the Tiara bioprosthesis was performed by a multidisciplinary team including 2 interventional cardiologists, a cardiac surgeon, and an echocardiographer, through a small subxyphoid incision. The atrial portion of the Tiara (the atrial “skirt”) is deployed first so that the flat aspect of the prosthesis frame is oriented anteriorly to align with the D-shaped mitral annulus, followed by deployment of the ventricular portion of the prosthesis that anchors behind the native anterior and posterior mitral leaflets (Fig. 2).

Under general anesthesia and mechanical ventilation, a small subxyphoid incision (<5 cm) was performed exposing the LV apex to allow apical puncture. One orthogonal U-shaped (purse string) suture was placed around the apical entry site. Unfractionated heparin (100 IU/kg) and lidocaine (1 mg/kg) were administered intravenously before apical cannulation. After apical puncture and sheath insertion, a 6-F pigtail catheter and a J-tipped 0.035-inch guide wire were inserted and then advanced across the mitral apparatus into the left atrium. Following removal of the pigtail catheter, the Tiara bioprosthesis, loaded in its delivery system, was advanced over the guidewire and positioned in the left atrium. Upon angiographic and echocardiographic confirmation of proper central positioning within the mitral planes, the guidewire was removed. Tiara implantation began with deployment of the atrial skirt to fit the D-shaped mitral annulus so that the flat aspect of the prosthesis frame was aligned with the LV outflow tract and the aorta. Accurate alignment and engagement of the flat aspect of the Tiara bioprosthesis with the anterior side of the mitral annulus was directed by echocardiography and guided by fluoroscopy utilizing special radiopaque markers on the metal frame of the prosthetic valve. Once aligned and seated on the atrial side of the mitral annulus, the ventricular portion of the prosthesis was deployed and anchored behind the native anterior and posterior mitral leaflets. Immediately

Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tr>
<td>LV</td>
<td>left ventricle/ventricular</td>
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<tr>
<td>MR</td>
<td>mitral regurgitation</td>
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<td>MV</td>
<td>mitral valve</td>
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<td>PVL</td>
<td>paravalvular leak</td>
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<td>TAMI</td>
<td>transapical mitral implantation</td>
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following the final launch of the Tiara, the delivery system was removed, and hemostasis was secured with the previously placed apical purse string.

A final echocardiographic, hemodynamic, and angiographic evaluation was performed to document mitral prosthesis function, valvular or paravalvular regurgitation, aortic and tricuspid valve function, presence of an LV outflow tract gradient, ventricular function, and patency of the left coronary circulation.

Short-term animal model. The purpose of the short-term model was to assess the safety and feasibility of Tiara implantation, to test several implantation techniques, and to make minor modifications and alterations in the design of the prosthesis frame and delivery system. Healthy domestic swine (mean weight 65 kg) were used, with a follow-up of 90 min to 96 h post-implantation. All animals with a successful implantation were monitored hemodynamically for a minimum of 90 min, at which time an echocardiographic evaluation was performed. All but 7 animals were euthanized immediately after the 90-min follow-up. These 7 animals were selected randomly from the pigs with no MR or paravalvular leak (PVL). These animals that were allowed to survive were extubated and allowed to recover from anesthesia, and then monitored clinically for 4 to 96 h before they were sacrificed. All hearts were explanted for macroscopic evaluation.

Long-term animal model. A normal ovine animal model (mean weight 69 kg) was used to test and evaluate the long-term performance of the implanted Tiara valve. The sheep model is considered the gold standard for long-term testing for valve implantation because the tissue leaflets are more prone to calcification and destruction. The mitral annulus size is comparable to an adult human and does not change significantly over the 5-month period compared with the swine model. The dimensions of the Tiara bioprosthesis used in this animal experiment were 29 × 35 mm.

Following successful implantation, the animals were allowed to recover and then sent back to the farm. At 30 days (±14 days), 90 days (±14 days), and 120 days (±14 days), animals underwent follow-up evaluations that included clinical assessment, tests for complete blood count and chemistry, (including lactate dehydrogenase), echocardiography and rotational cineangiography of the heart to evaluate the positioning and function of the bioprosthesis and to detect fractures and deformations of the frame of the Tiara.
Final evaluation was performed at 150 ± 14 days post-TAMI. Under general anesthesia, right and left heart catheterization with hemodynamic evaluation was performed followed by LV and aortic root angiography and left coronary angiography. Immediately after catheterization, the sternum was opened, and a transepicardial echocardiogram was performed. Subsequently, the animals were euthanized, and an in situ cardioscopy of the saline-filled heart was performed. The Tiara valves were analyzed with high-quality digital x-ray imaging (Faxitron MX-20, Faxitron Bioptics, Tucson, Arizona) to detect microcalcification of the leaflets, as well as fractures in the metal frame. Finally, the hearts were harvested for macroscopic and microscopic evaluation.

Human cadaver model. Because of the substantial anatomic differences between the healthy porcine and ovine hearts and the diseased human heart with severe MR, the human cadaveric model was used to test the suitability of the Tiara bioprosthesis for the anatomy of the human heart. Even though the Tiara was tested extensively and successfully in 2 different animal models, because it is intended eventually to treat humans with severe MR and not healthy pigs or sheep, it was important to test its fittingness in this human model.

The cadaver model was used to test alignment, positioning, and anchoring of the Tiara valve in human cadaver hearts. A total of 24 hearts were studied. The hearts used were freshly defrosted hearts without any fixation, so the valve leaflets were pliable.

Transapical implantations of the Tiara valves were performed in both normal human hearts and in hearts of patients with a history of severe MR, with and without LV dilation, with and without aortic valve regurgitation. Alignment of the Tiara in the native mitral apparatus and the achievement of proper positioning and anchoring were assessed using 2 endoscopic video cameras positioned in the left atrium and in the LV of saline-filled hearts. The Tiara valve implantation was performed using a pulsatile model with manual stimulation to replicate ventricular contractions and leaflet motion.

Results

Short-term animal model. During the time course of the short-term animal model, minor alterations and variations of the Tiara were tested, and the most suitable version of the Tiara valve was used for the long-term animal model. The results in part of the short-term animal experiments were previously published (10).

Tiara valves were successfully implanted in 29 of the 36 (81%) animals.Implantation was unsuccessful in 7 animals because of improper positioning of the valve (n = 3), failure
of the valve anchors to properly engage during deployment (n = 2), and ventricular fibrillation (n = 2). The total procedure time from thoracotomy to prosthesis deployment ranged from 17 to 26 min. The implantation time from apical access to closure ranged from 5 to 13 min. None of the valves migrated or embolized during or after implantation. There was an evolution and refinement of the implantation procedure and of the device over the course of these 36 animals. There was a steady increase in the rate of successful implantations as the series progressed, with the final 12 animals in the series all undergoing a successful and uneventful implantation.

All of the 29 animals that underwent a successful Tiara implantation remained hemodynamically stable throughout the procedure. Self-limited bouts of atrial fibrillation were occasionally noted when the valve was manipulated within the left atrium, but no sustained or hemodynamically relevant arrhythmias occurred after implantation. Postprocedural cardiac catheterization in these animals demonstrated widely patent circumflex coronary arteries and no discernible LV outflow tract gradient. Transesophageal echocardiography confirmed good function and alignment of all valves and leaflets, with no LV outflow tract obstruction, encroachment on the aortic valve, or transvalvular gradients. A significant PVL was only present in animals showing a mismatch between the MV annulus size and the prosthesis diameters. None of the last 8 animals had any significant PVL. Macroscopic evaluation of the explanted hearts demonstrated stable and secure positioning of the prostheses in both vertical and horizontal planes of the mitral annulus, without evidence of traumatic injuries to the ventricular or the atrial walls.

**Long-term animal model.** Seven animals were evaluated 150 ± 14 days post-Tiara implantation. A summary of the long-term echocardiographic and hemodynamic evaluation is presented in Table 1. All 7 animals had been clinically stable, maintaining sinus rhythm and normal behavior throughout the follow-up, without signs of cardiovascular decompensation. Echocardiographic assessment demonstrated that all Tiara bioprostheses were well positioned, properly aligned with the flat aspect of the D-shape facing the aorta, with excellent leaflet motion and coaptation (Fig. 3). Five of the 7 animals had no MR through the prosthctic valve, and 2 had a mild degree of valvular MR. Six of the 7 animals had a mild or moderate PVL, and 1 animal had no PVL (Table 1). None of the animals developed a significant pressure gradient across the mitral prosthesis or in the LV outflow tract and the aortic valve, and none developed elevated pulmonary pressure or tricuspid valve regurgitation. None had pericardial fluid accumulation. Angiographically, all of the bioprostheses were properly positioned and secured. Five animals had a mild or moderate degree of MR (valvular and paravalvular), and 2 had none (Table 2). Coronary angiography at 150 days post-TAMI revealed patent coronary arteries without impingement on the circumflex coronary artery (Fig. 4), normal LV size and function, and normal pulmonary artery and right-side pressures. Aortic root angiography ruled out the presence of aortic valve regurgitation in all animals.

The degree of PVL in all long-term animals was such that it did not have any hemodynamic significance, and also, it did not cause any degree of hemolysis, as assessed by the complete blood counts and lactate dehydrogenase levels at follow-up compared with the baseline levels.

As only 1 size of Tiara valve was available for implantation, it is thought that the PVL observed is attributable to the size mismatch between the native annulus and prosthetic device. In all animals, LV wall motion and overall function were normal. High-quality digital x-ray imaging (Faxitron MX-20) did not reveal any deformations of the metal frame struts.

In situ cardiocopy showed homogenous coverage of the metal struts with a white fibrotic connective tissue layer, both along the atrial and ventricular struts. Positioning of the prosthesis was stable and secure, both in the vertical and horizontal planes of the mitral annulus, without evidence of

<table>
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<tr>
<th>Table 1. Echocardiographic Evaluation of the 7 Long-Term Animals, 150 Days Post-Tiara Implantation</th>
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<tr>
<td>Animal</td>
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<td>1</td>
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<td>2</td>
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<td>3</td>
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<td>4</td>
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<td>5</td>
</tr>
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<td>6</td>
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<td>7</td>
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*Regurgitation severity: 0 = trace/mild; 1 = moderate; 2 = moderate to severe; 4 = severe; |Pericardial fluid amount estimation: 0 = none; 1 = small; 2 = moderate; 3 = large/tamponade. |

AR = aortic regurgitation; LVOT = left ventricular outflow tract; LVWMA = left ventricular wall motion abnormality; MR = mitral regurgitation; NSR = normal sinus rhythm; PVL = paravalvular leak; TR = tricuspid regurgitation.
traumatic injuries to the ventricular or the atrial walls. The prosthesis leaflets were freely mobile, supple, and without evidence of fibrous deposits, clots, or calcifications.

Macroscopic and microscopic evaluation demonstrated that the devices appeared well seated; all valve frames showed good incorporation by a thin pannus around the atrial and ventricular surfaces with fibrous tissue growth adequate for healing. The pannus was composed of dense, well-organized smooth muscle cells/fibroblasts in a collagenous matrix around the device components. The pericardial leaflets were intact without tears or perforations. There was no evidence of endocarditis or leaflet calcification, and the myocardium adjacent to the device showed mild compression in some areas without necrosis or significant inflammation (Figs. 5 and 6).

**Human cadaver implantation.** A total of 24 hearts were studied, 17 female hearts and 7 male hearts; the age range was 58 to 94 years, body weight range was 36 to 87 kg (mean 62 kg), and body height range was 122 to 183 cm (mean 160 cm). Twelve hearts had moderate or severe mitral regurgitation, 7 hearts had congestive heart failure, and 5 were normal hearts. Transapical implantation of Tiara valves was performed under direct visual guidance using ventricular and atrial endoscopic video cameras in saline-filled hearts. Proper orientation of the asymmetric atrial portion of the Tiara valve as well as appropriate engagement and position of the ventricular anchoring system were confirmed first by direct vision on video monitor screens and later by macroscopic evaluation after dissection of the left atrial wall and opening the LV wall. The implantation

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**Table 2. Cardiac Catheterization Evaluation of the 7 Long-Term Animals, 150 Days Post-Tiara Implantation**

<table>
<thead>
<tr>
<th>Animal</th>
<th>MR (0–4)*</th>
<th>Coronary Artery Obstruction</th>
<th>AR (0–4)*</th>
<th>LVOT Gradient</th>
<th>LV Function</th>
<th>Valve Deformation or Significant Frame Fracture</th>
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<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>No</td>
<td>0</td>
<td>0</td>
<td>Good</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>No</td>
<td>0</td>
<td>0</td>
<td>Good</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>No</td>
<td>0</td>
<td>0</td>
<td>Good</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>No</td>
<td>0</td>
<td>0</td>
<td>Good</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>No</td>
<td>0</td>
<td>0</td>
<td>Good</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>No</td>
<td>0</td>
<td>0</td>
<td>Good</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>No</td>
<td>0</td>
<td>0</td>
<td>Good</td>
<td>No</td>
</tr>
</tbody>
</table>

*Regurgitation severity: 0 = trace/mild; 1 = mild; 2 = moderate; 3 = moderate to severe; 4 = severe.

LV = left ventricular; other abbreviations as in Table 1.
resulted in appropriate geometric positioning with full circumferential coverage of the atrial aspect of the mitral annulus and proper orientation of the D shape (Fig. 7), and good apposition and location of the ventricular anchoring system. Orientation, alignment, and stable anchoring were achieved both in normal hearts and in dilated hearts with heart failure or MR.

**Discussion**

The pre-clinical assessment of the safety and feasibility of implantation of the Tiara transcatheter bioprosthetic mitral valve, including the short-term and long-term performance, was successful.

Using the porcine short-term animal model, we have confirmed the feasibility and short-term safety of Tiara implantation. In addition, we have developed a rapid and straightforward implantation procedure resulting in a stable and well-aligned functional bioprosthesis. Macroscopic evaluation of the explanted hearts demonstrated stable and secured positioning of the valves in all planes of the mitral apparatus, without evidence of traumatic injuries to the ventricular or the atrial wall. These short-term results were encouraging and paved the way for long-term animal model experiments and subsequent human cadaver implantations.

At 150 days after Tiara implantation, all 7 long-term animals exhibited normal clinical status and behavior without any signs of heart failure. There was no significant MR observed, and the LV function was normal in all. The metal frames were homogeneously covered with a fibrous tissue on both sides of the mitral annulus, suggesting proper healing without any visible signs of inflammation. The concerns regarding potential long-term deterioration of prosthesis functionality and integrity were answered as no deformation of the metal frame was seen, the prosthesis leaflets were mobile and free of clots, and there was no macro- or microcalciﬁcation up to 150 days post-implantation.

Transcatheter MV implantation has the potential to become the preferred intervention to treat severe MR in patients who are at high risk for surgery, because it can theoretically reduce MR to an extent similar to that of...
surgery while preserving the mitral apparatus. However, many challenges need to be addressed in the design and development of a device to be deployed across an asymmetric and multi-planar MV annulus. The ideal device must be stable and resistant to displacement or migration while enduring continuous cyclical movements of the mitral annulus and the base of the heart, as well as the high pressure gradients that are generated across the mitral valve. Valve materials must be durable enough to withstand the loads generated. Because regurgitation is poorly tolerated in the mitral position, valvular regurgitation and PVL after the implantation must be minimized. Additionally, the valve must not obstruct the LV outflow tract, occlude the circumflex coronary artery, or compress the coronary sinus. Ideally, the valve should minimize conduction system disruption. Transcatheter MV implants should restore unidirectional flow, spare chordal structures, and leave adjacent myocardium intact while minimizing the risks associated with the procedure, allowing high-risk patients and those who are not candidates for surgery to receive definitive treatment.

The Tiara is a catheter-based mitral valve bioprosthesis intended for the treatment of patients with symptomatic severe MR who are not candidates for mitral valve surgery. The Tiara utilizes cross-linked bovine pericardial tissue leaflets mounted inside a self-expanding metal alloy frame and crimped onto a short, flexible 32-F delivery catheter for transapical delivery. The tricuspid bioprosthetic Tiara was specifically designed to fit the complex anatomic structure of the mitral apparatus. It fits the area of the left atrium surrounding the mitral annulus and engages the mitral leaflets and chordae within the LV so it is secured from anterograde or retrograde dislodgement. The assembly of the Tiara valve is shaped to match the natural orifice of the MV and to avoid post-implantation impingement on the LV outflow tract and on the coronary blood vessels.

On the basis of our short-term and long-term animal results and our early human ex vivo experiments, we have demonstrated that the Tiara frame geometrically fits the anatomy and shape of the native mitral annulus without impinging on the LV outflow tract or circumflex artery. Due to its self-expanding properties, the PVL observed should be minimized with proper annulus–prosthesis match. The device is well anchored, yet maintains the functional complexity and integrity of the subvalvular apparatus, which is an important characteristic of myocardial contractility, especially in patients with reduced ejection fraction and decreased contractility.

Study limitations. The Tiara valve is a prototype, and there are limitations inherent to this proof-of-concept study. First, the Tiara was designed and built to fit human hearts with severe MR. Tiara has not been tested in a long-term MR model where both the left atrium and ventricle are dilated. Testing it in the hypercontractile normal sheep heart with a small LV and small left atrium is problematic because the anatomy and behavior of the model is different from that of the intended target. No doubt that for human implantation more advanced imaging modalities will be used to better guide the TAMI procedures. These advanced imaging
modalities will include online Doppler and 3-dimensional transesophageal echocardiography, as well as 3-dimensional/4-dimensional computed tomography angiography.

Second, the Tiara was available in 1 annular size, and native annulus–prosthesis mismatch could not be avoided in some cases, despite tight criteria for animal selection. These 2 major limitations are the cause of the mild-to-moderate degree of PVL observed. Finally, because Tiara is a self-expanding valve, it is unknown how the system will behave in a partially or severely calcified mitral apparatus. Incomplete prosthesis apposition against the myocardial structures is known to cause PVL with transcatheter aortic valve implantation. A similar situation remains possible with the Tiara valve, which calls for careful selection of clinical cases for the initial human clinical trials.

Conclusions

The Tiara is a catheter-based MV bioprosthesis intended for the treatment of patients with symptomatic severe MR who are high surgical risk candidates for open MV surgery. The results of our short-term and long-term pre-clinical experimentation with the Tiara transcatheter self-expanding mitral bioprosthetic valve are encouraging. We have demonstrated that the implantation of the Tiara valve in healthy swine and sheep is feasible and safe. Tiara implantation resulted in a stable and well-functioning MV bioprosthesis, for up to 150 days of follow-up. The durability, functionality, leaflet pliability, and lack of leaflet calcification, as well as tissue coverage of the metal frame, were all verified in the long-term animal experiments. The results of the on-going pre-clinical experiments of the Tiara valve will hopefully lead the way to human clinical trials.

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REFERENCES


Key Words: mitral regurgitation • mitral valve • mitral valve implantation • transapical • transcatheter.