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## Trans Apical Mitral Implantation (TAMI) of the Tiara™ Bio-prosthesis: Pre-Clinical Results

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Short title: Trans Apical Mitral Implantation of the Tiara™

**Disclosure:**

Dr Shmuel Banai is the Medical Director of Neovasc Inc

Drs Christopher J. White, Elazer Edelman are consultants for Neovasc Inc,

Stefan Verheye and E. Marc Jolicoeur are unpaid PI's of the COSIRA (coronary sinus Reducer) clinical trial

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None of the other authors have any conflict of interest.

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**Abstract**

**Objectives:** To describe the pre-clinical evaluation of Trans-Apical Mitral Implantation (TAMI) of the Tiara in preparation for first-in-man implantation.

**Background:** The Tiara™ is a trans-catheter self-expanding mitral bio-prosthesis, specifically designed for the complex anatomical configuration of the mitral apparatus.

**Methods:** Tiara valves were implanted in an acute porcine model, in a chronic ovine model, and in human cadavers.

**Results:** Acute and chronic evaluation demonstrated excellent function and alignment of the valves, with no left ventricular outflow tract (LVOT) obstruction, coronary artery obstruction, or trans-valvular gradients. Chronic evaluation of 7 sheep demonstrated clinically stable animals. A mild degree of prosthetic valve regurgitation was seen in 2 of the 7 sheep. Mild to moderate degree of para-valvular 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 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 trans-catheter mitral valve implantation we report the successful pre-clinical evaluation of the Tiara trans-catheter self-expanding mitral bioprosthetic valve. In porcine and ovine models without mitral regurgitation, trans-apical mitral implantation of the Tiara valve is technically feasible, safe, and results in a stable and well-functioning mitral bioprosthesis.

**Key words:** mitral valve, mitral regurgitation, Mitral valve implantation, trans apical, trans catheter

**Condensed Abstract:** We describe the pre-clinical evaluation of the Tiara, a trans-catheter self-expanding mitral bio-prosthesis, in acute and chronic animal models, and in a human cadaveric model. Excellent function and alignment of the valves were demonstrated, with no LVOT or coronary obstruction, and or trans-valvular gradients. In the chronic model a mild degree of prosthetic valve regurgitation was seen in 2 of the 7 sheep. In human cadaver hearts, proper anatomic alignment and anchoring of the Tiara were demonstrated.

Pre-clinical evaluation show that trans-apical mitral implantation of the Tiara is feasible, safe, and results in a stable and well-functioning mitral bioprosthesis.

**Abbreviations:**

TAMI –	Trans Apical Mitral Implantation
MV –	mitral valve
MR –	mitral regurgitation
PVL –	para-valvular leak
PAP –	pulmonary artery pressure
MVG –	mitral valve gradient
LVOT –	left ventricular outflow tract
TR –	tricuspid regurgitation
AR –	aortic regurgitation

## Introduction

Severe mitral regurgitation (MR) is commonly associated with dilatation of the heart and advanced coronary artery disease ultimately resulting in disability and death from congestive heart failure. While surgery remains the gold standard treatment for mitral regurgitation, approximately one third of potential candidates are considered to be at too high risk for surgical repair or replacement.(1,2,3) Severe mitral regurgitation 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 mitral regurgitation is expected to rise dramatically.(4)

Various novel percutaneous trans-catheter 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 a by hybrid approach through the left atrium, the chordae - percutaneous chordal implantation, or the LV - percutaneous LV remodeling. The percutaneous edge-to-edge repair technology has been shown to be non-inferior to open repair in a randomized clinical trials. However, percutaneous mitral valve repair is not possible for many patients, and therefore, MV replacement may be an attractive alternative.(5,6) Several trans-catheter MV implantation (TMVI) technologies, either trans-apical or trans-septal are in various stages of pre-clinical evaluation.(7,8,9)

The Tiara™ is a catheter-based self-expanding mitral bio-prosthesis, specifically designed to fit the complex anatomical structure of the mitral apparatus. It is implanted using a trans-apical 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™ in acute and chronic animal models, as well as in human cadaver hearts, performed as part of the preparation for the planned “first-in-man” trans-apical 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 crimped onto a short flexible 32F delivery catheter for trans-apical delivery (Figure 1). A retractable sheath retains the valve in place until deployment. The atrial portion engages the area of the left atrium (LA) surrounding the mitral annulus and a series of anchoring structures actively engage the mitral leaflets and chordae within the left ventricle, 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, re-position, and restart the implantation process. Tiara implantation, orientation and alignment was performed under simultaneous echocardiographic and fluoroscopic guidance using specific radiopaque set of markers on the nitinol frame and on the delivery system.

### **Tiara Implantation Protocols**

The animal protocols were approved by the Montreal Heart Institute’s Animal Care & Use Committee, and the Animal Care & Use Committee of the Institute Mutualiste Montsouris Recherche, Paris, France. The protocol for human cadaver trials was approved by the Seattle Science Foundation, Seattle, WA, USA.

Trans-apical implantation of the Tiara™ was performed by a multi-disciplinary team including two interventional cardiologists, a cardiac surgeon and an echocardiographer, through a small sub-xyphoid incision. The atrial portion of the Tiara™ (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 which anchors behind the native anterior and posterior mitral leaflets, Figure 2.

Under general anesthesia and mechanical ventilation, a small sub-xyphoid incision (<5cm) 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 prior to apical cannulation. After apical puncture and sheath insertion, a 6F pigtail catheter and a J tipped 0.035 inch guide wire were inserted and advanced across the mitral apparatus into the left atrium. Following removal of the pigtail catheter, the Tiara™ loaded into its delivery system was advanced over the guide wire and positioned in the LA. Upon angiographic and echocardiographic confirmation of proper central positioning within the mitral planes, the guide wire 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 with the anterior side of the mitral annulus was directed by echo 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 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 para-valvular regurgitation, aortic and tricuspid valves function, presence of an LV outflow tract gradient, ventricular function, and patency of the left coronary circulation.

#### Acute Animal Model:

The purpose of the acute 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 minutes to 96 hours post implantation. All animals with a successful implantation were monitored hemodynamically for a minimum of 90 minutes, at which time an echocardiographic evaluation was performed. All but 7 animals were euthanized immediately after the 90 minute follow-up. These 7 animals were selected randomly from the pigs with no MR or PVL. These animals that were allowed to survive were extubated and allowed to recover from anesthesia and monitored clinically for 4 - 96 hours before they were sacrificed. All hearts were explanted for macroscopic evaluation.

#### Chronic 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™. The sheep model is considered the gold standard for long-term testing for valve implantation, as 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 to the swine model. The dimensions of the Tiara used in this animal experiment were 29x35mm.

Following successful implantation the animals were allowed to recover and sent back to the farm. At 30 days ( $\pm 14$  days), 90 days ( $\pm 14$  days) and 120 days ( $\pm 14$  days) animals underwent follow-up evaluations which included clinical assessment, blood tests for CBC chemistry including LDH, 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  $150 \pm 14$  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 trans-epicardial 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) to detect micro-calcification 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 anatomical 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 to the anatomy of the human heart. Even though the Tiara was tested extensively and successfully in 2 different animal models, since 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 model.

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

Trans-apical 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 left ventricular dilatation, with and without aortic valve regurgitation. Alignment of the Tiara™ in the native mitral apparatus and achieving proper positioning and anchoring were assessed using 2 endoscopic video cameras positioned in the left atrium and in the left ventricle of saline-filled hearts. The Tiara implantation was performed using a pulsatile model with manual stimulation to replicate ventricular contractions and leaflet motion.

## Results

**Acute Animal Model:** During the time course of the acute animal model, minor alterations and variations of the Tiara™ were tested, and the most suitable version of the Tiara™ was used for the chronic animal model. The results of the acute animal experiments were previously published in part.(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 minutes. None of the valves migrated or embolized during or after implantation. There was an evolution and refinement of the implantation procedure techniques and of the device over the course of these 36 animals.

There was a steady increase in the rate of successful implantation 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. Post procedural cardiac catheterization in these animals demonstrated a widely patent circumflex coronary arteries and no discernible LV outflow tract gradient. TEE confirmed good function and alignment of all valves and leaflets, with no LV outflow tract obstruction, encroachment on the aortic valve, or trans-valvular gradients. A significant paravalvular leak (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.

**Chronic Animal Model:** Seven animals were evaluated  $150 \pm 14$  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™ bio-prostheses were well positioned, properly aligned with the flat aspect of the "D" shape facing the aorta, with excellent leaflet motion and coaptation (Figure 3). Five of the 7 animals had no mitral regurgitation through the prosthetic valve, and 2 had a mild degree of valvular MR. Six of the 7 animals had a mild or moderate PVL, and one animal had no PVL (Table 1). None of the animals developed a significant pressure gradient

across the mitral prosthesis or in the left ventricular 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 para-valvular), and 2 had none (Table 2). Coronary angiography at 150 days post TAMI revealed patent coronary arteries without impingement on the circumflex coronary artery (Figure 4), normal left ventricular 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 para-valvular leak in all chronic 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 CBC and LDH levels at follow up compared with the baseline levels.

As only one 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 was normal. High-quality digital x-ray imaging (Faxitron MX-20) did not reveal any deformations of the metal frame struts.

In-situ cardioscopy showed homogeneous 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 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 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, (Figures 5 and 6).

**Human Cadaver Implantation:** A total of 24 hearts were studied, 17 female hearts and 7 male hearts, age range was 58-94 years, body weight range was 36-87 kg (mean- 62kg), body height range was 122-183cm (mean- 160cm). Twelve hearts had moderate and severe mitral regurgitation, 7 hearts had congestive hearts failure, and 5 were normal hearts. Trans-apical 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 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 left ventricular wall. The implantation resulted in appropriate geometrical positioning with full circumferential coverage of the atrial aspect of the mitral annulus and proper orientation of the "D" shape (Figure 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, feasibility, including the acute and chronic performance of the Tiara™ trans-catheter bio-prosthetic mitral valve, was successful.

Using the porcine acute 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 bio-prosthesis. 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 acute results were encouraging and paved the way for chronic animal model experiments and subsequent human cadaver implantations.

At 150 days after Tiara™ implantation, all 7 chronic animals exhibited normal clinical status and behavior without any signs of heart failure. There was no significant mitral regurgitation observed, and the left ventricular function was normal in all. The metal frames were homogeneously covered with a fibrous tissue in 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 micro-calcification up to 150 days post implantation.

Trans-catheter MV implantation has the potential to become the preferred intervention to treat severe mitral regurgitation in patients who are at high risk for surgery, since it can theoretically reduce mitral regurgitation 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. Since regurgitation is poorly tolerated in the mitral position, valvular regurgitation and paravalvular leaks 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. Trans-catheter mitral valve 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 bio-prosthesis intended for the treatment of patients with symptomatic severe mitral regurgitation who are not candidate 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 32F delivery catheter for trans-apical delivery. The tricuspid bio-prosthetic TIARA was specifically designed to fit the complex anatomical 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 left ventricle so it is secured from anterograde or retrograde dislodgement. The assembly of the TIARA is shaped to match the natural orifice of the mitral valve and to avoid post implantation impingement on the left ventricle outflow tract and on the coronary blood vessels.

Based upon our acute and chronic 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 LVOT or circumflex artery. Due to its self-expanding properties, the para-valvular leak observed should be minimized with proper annulus-prosthesis match. The device is well anchored, yet maintains the functional complexity and integrity of the

sub-valvular 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 of this proof-of-concept study.

First, the Tiara™ was designed and built to fit human hearts with severe mitral regurgitation.

Tiara has not been tested in a chronic mitral regurgitation model where both the left atrium and ventricle are dilated. Testing it in the hyper-contractile normal sheep heart with a small left ventricle and small left atrium is problematic since the anatomy and behavior of the model is different from that of the intended target. No doubt that for human implantation a more advanced imaging modalities will be used to better guide the TAMI procedures. These advanced imaging modalities will include on-line Doppler and 3D TEE as well as 3D/4D CT angiography.

Second, the Tiara™ was available in one 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 para-valvular leak observed. Finally, since 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 para-valvular leak with trans-catheter 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 mitral valve bio-prosthesis intended for the treatment of patients with symptomatic severe mitral regurgitation who are high surgical risk candidates for open mitral valve surgery. The results of our acute and chronic pre-clinical experimentation with the Tiara™ trans-catheter self-expanding mitral bio-prosthetic 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 mitral valve bio-prosthesis, for up to 150 days of follow up. The durability, functionality, leaflet pliability, lack of leaflet calcification, as well as tissue coverage of the metal frame, were all verified in the chronic 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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**Figure legends****Figure 1: Tiara and delivery system**

Front and profile views of the Tiara (upper panel). The "D" shape of the valve, the atrial "skirt" which engages the atrial aspect of the mitral annulus, and the saddle shaped valve are clearly seen. Trans-apical delivery system (lower panel)

**Figure 2: Implantation sequence of the Tiara**

A: The CS wire outline the MV annulus. The pigtail catheter is anteriorly, in the ascending aorta, delivery system is through the mitral annulus into the left atrium  
 B: Atrial skirt is starting to open in left atrium, the flat aspect of the 'D' shaped Tiara are facing anteriorly  
 C: Atrial skirt is open and positioned on the atrial aspect of the mitral annulus, and the ventricular portion of the Tiara is delivered into position just before valve final release  
 D: Final release of the Tiara, before removal of the delivery system

**Figure 3: 3D echocardiogram of the implanted Tiara™ 150-days post implantation**

The "D" shaped Tiara™ is clearly seen. Left - the Tiara™ is closed during systole and the three leaflets are seen. Right - Tiara™ is open during diastole and the native aortic valve is closed

**Figure 4: Coronary angiography and left ventriculography 150 days post Tiara™ implantation**

Left: Patent coronary arteries, without evidence of impingement or obstruction of the left circumflex coronary artery are shown  
 Right: Left ventriculography in a sheep 150 days following TAMI

**Figure 5: Ventricular view of the Tiara™ 150 days after implantation in sheep's heart**

The papillary muscles (held by clamps), chordae tendineae and the sub-valvular mitral apparatus are intact. Valve frames are covered with fibrous tissue growth adequate for healing. Pericardial leaflets are intact without tears or perforations, there was no evidence of endocarditis or leaflet calcification, and the myocardium adjacent to the device is intact

**Figure 6: Atrial view of the Tiara™ 150 days after implantation in sheep's heart**

Picture was taken after the roof of the atrial wall was removed. The atrial "skirt" of the Tiara™ is well seated on the atrial aspect of the mitral annulus. Valve frames are covered with fibrous tissue growth adequate for healing. Pericardial leaflets are intact without tears or perforations; there was no evidence of endocarditis or leaflet calcification. The adjacent atrial wall is intact and free of inflammation or necrosis.

**Figure 7: Atrial view of the Tiara™ implanted in a human cadaver heart with history of severe mitral regurgitation.**

The atrial "skirt" of the Tiara™ is well seated on the atrial aspect of the mitral annulus. The Tiara is aligned so that the flat aspect of the "D" shaped Tiara™ is properly facing the aortic-mitral curtain.

**Table 1:** Echocardiographic evaluation of the 7 chronic animals, 150-days post TIARA implantation.

Echocardiographic assessment 150 days post TIARA implantation								
animal	Heart Rhythm	PVL (0-4)	MR (0-4)	TR (0-4)	LVOT gradient	AR (0-4)	Pericardial fluid (0-3)	LVWMA
1	NSR	0	0	0	0	0	0	no
2	NSR	2	0	0	0	0	0	no
3	NSR	2	0	0	0	1	0	no
4	NSR	1	1	0	0	0	0	no
5	NSR	1	1	1	0	0	0	no
6	NSR	1	0	0	0	0	0	no
7	NSR	2	0	0	0	0	0	no

Regurgitation severity: 0=trace/mild, 1=mild, 2=moderate, 3=moderate to severe, 4=severe

Pericardial fluid amount estimation: 0=none, 1=small, 2=moderate, 3=large/tamponade

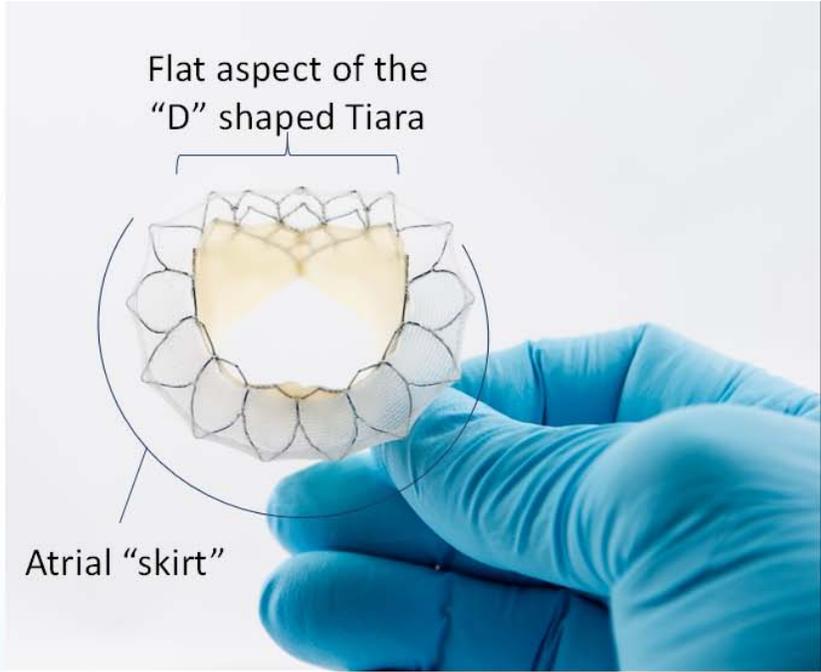
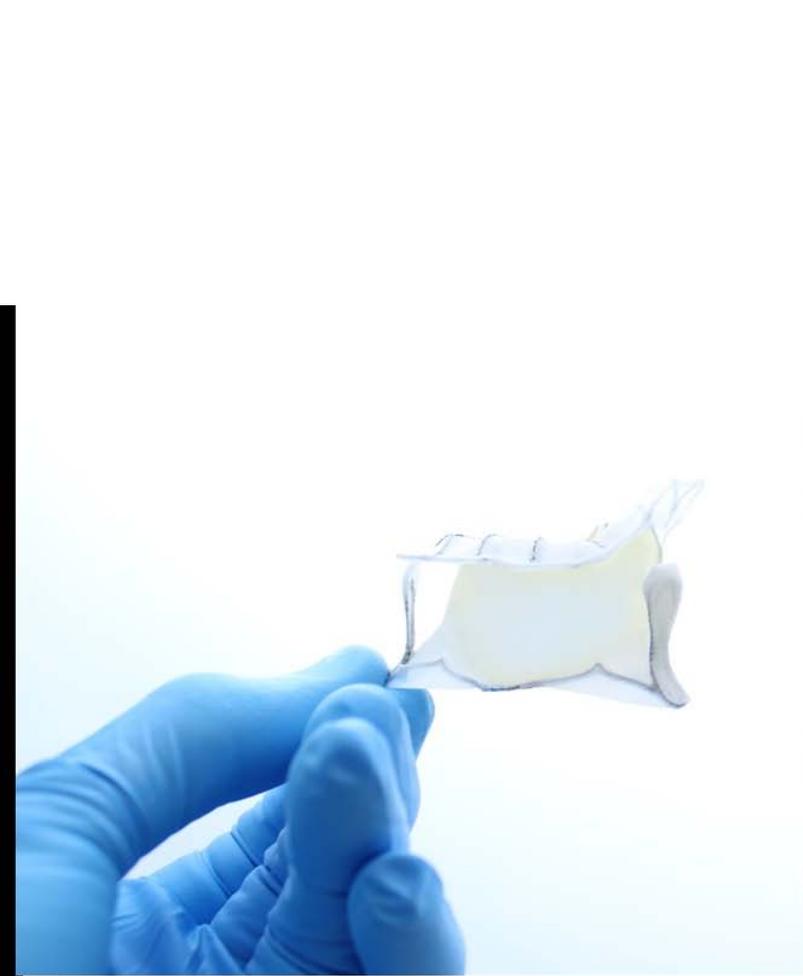
Abbreviations: PVL= par-valvular leak, MR=mitral regurgitation, TR=tricuspid regurgitation, LVOT=left ventricular outflow tract, AR=aortic regurgitation, LVWMA=left ventricular wall motion abnormality

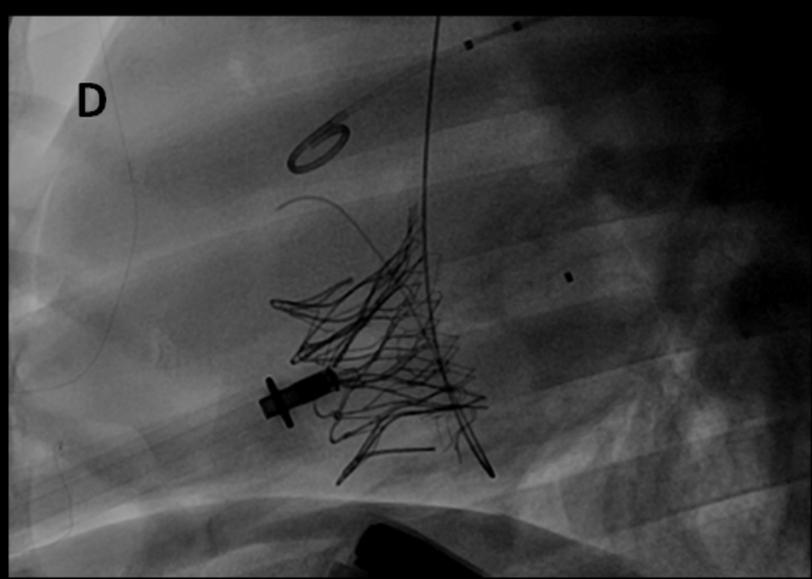
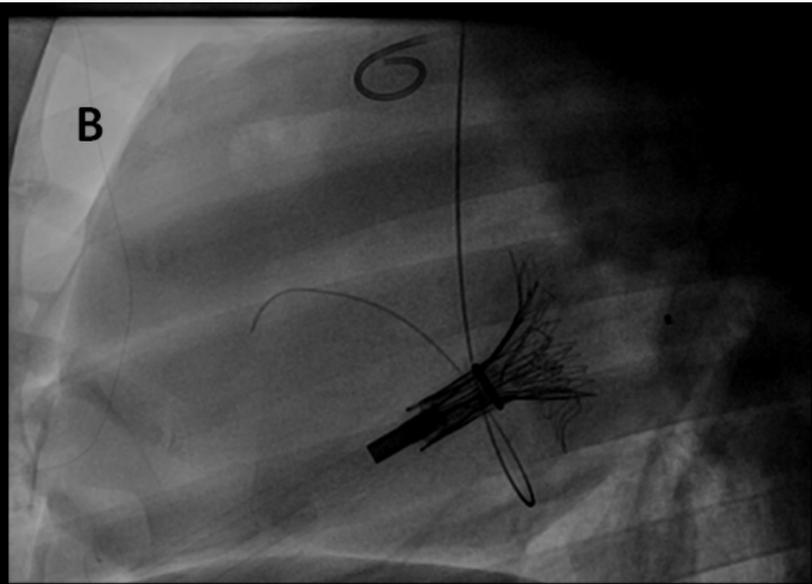
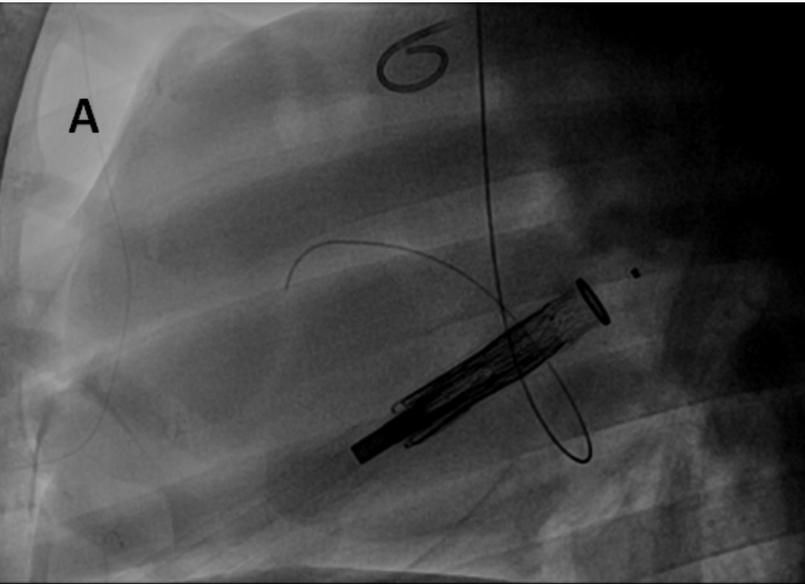
**Table 2:** Cardiac catheterization evaluation of the 7 chronic animals, 150-days post TIARA implantation.

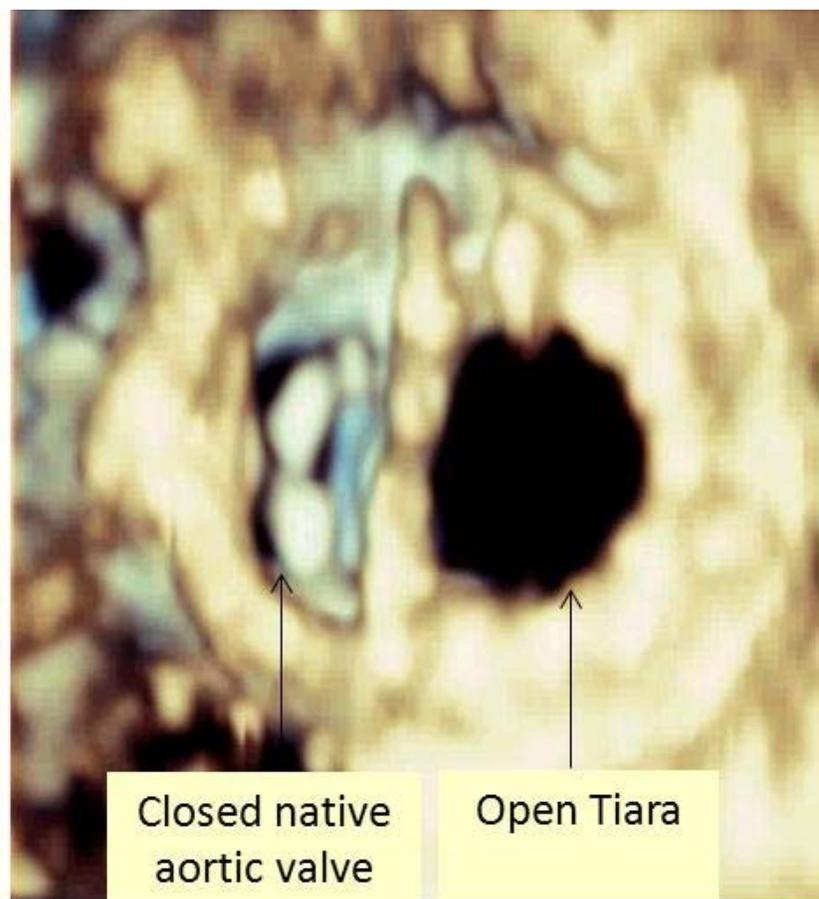
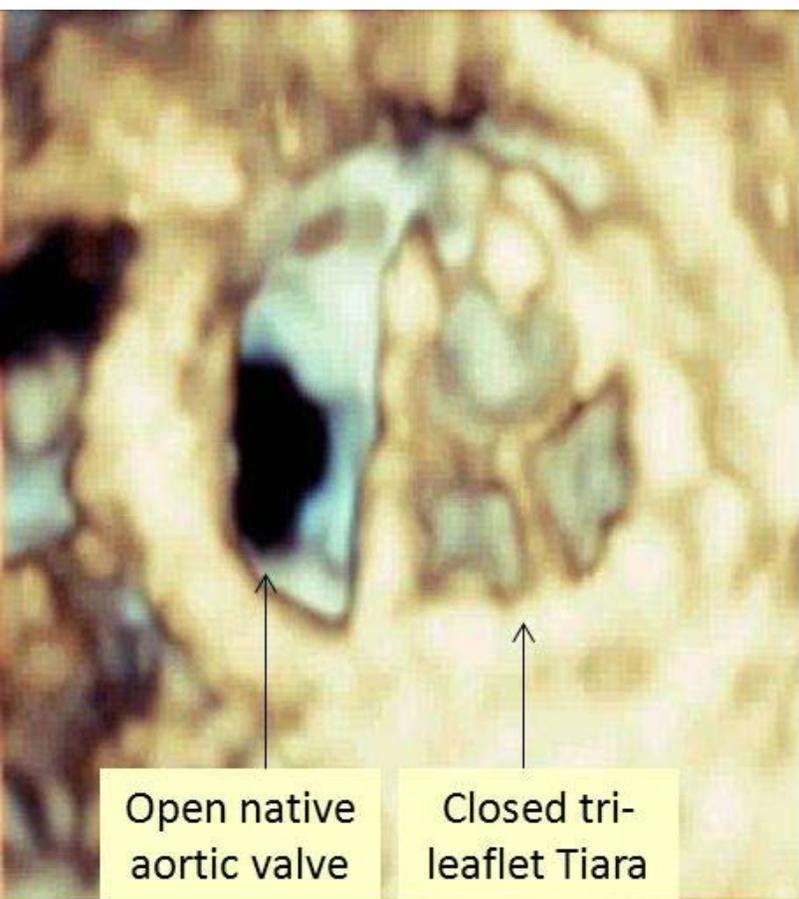
Cardiac catheterization assessment 150 days post TIARA implantation						Digital x-ray
animal	MR (0-4)	coronary artery obstruction	AR (0-4)	LVOT gradient	LV function	Valve deformation or significant frame fracture
1	0	no	0	0	good	no
2	1	no	0	0	good	no
3	0	no	0	0	good	no
4	2	no	0	0	good	no
5	2	no	0	0	good	no
6	2	no	0	0	good	no
7	2	no	0	0	good	no

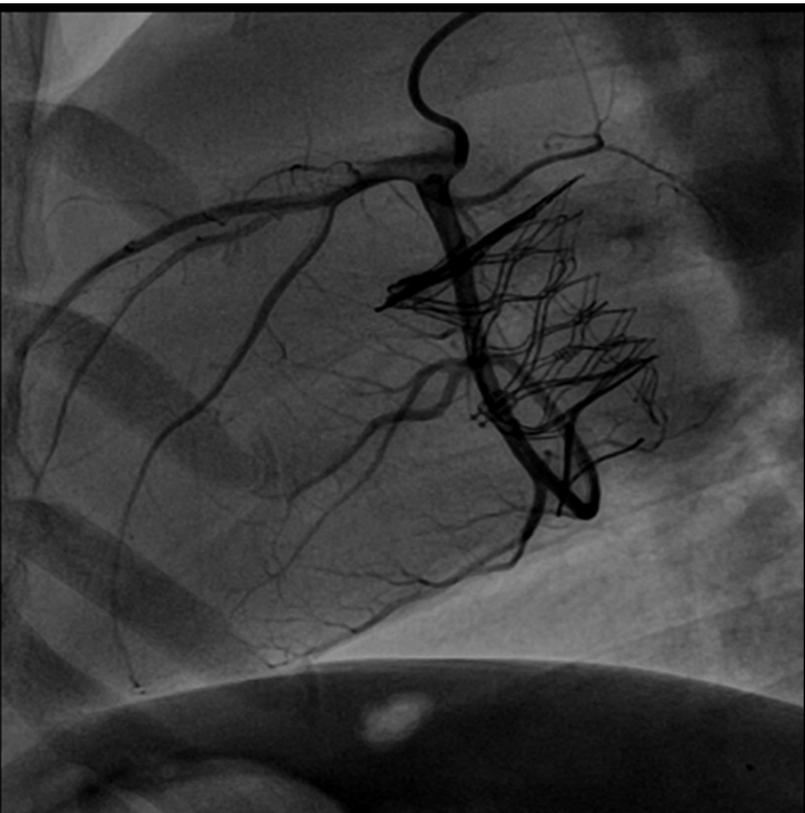
Regurgitation severity: 0=trace/mild, 1=mild, 2=moderate, 3=moderate to severe, 4=severe

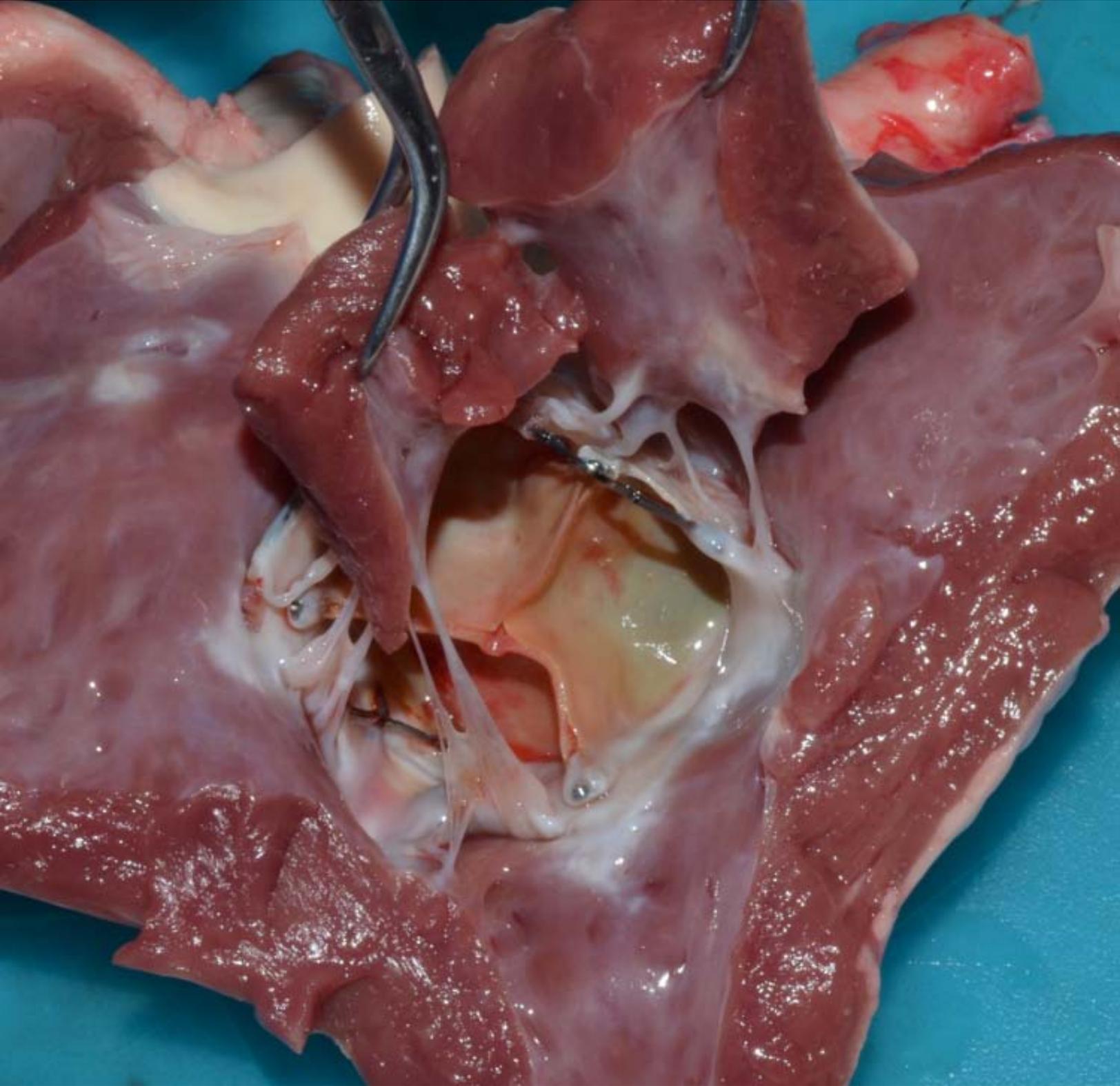
Abbreviations: MR=mitral regurgitation, AR=aortic regurgitation, LVOT=left ventricular outflow tract

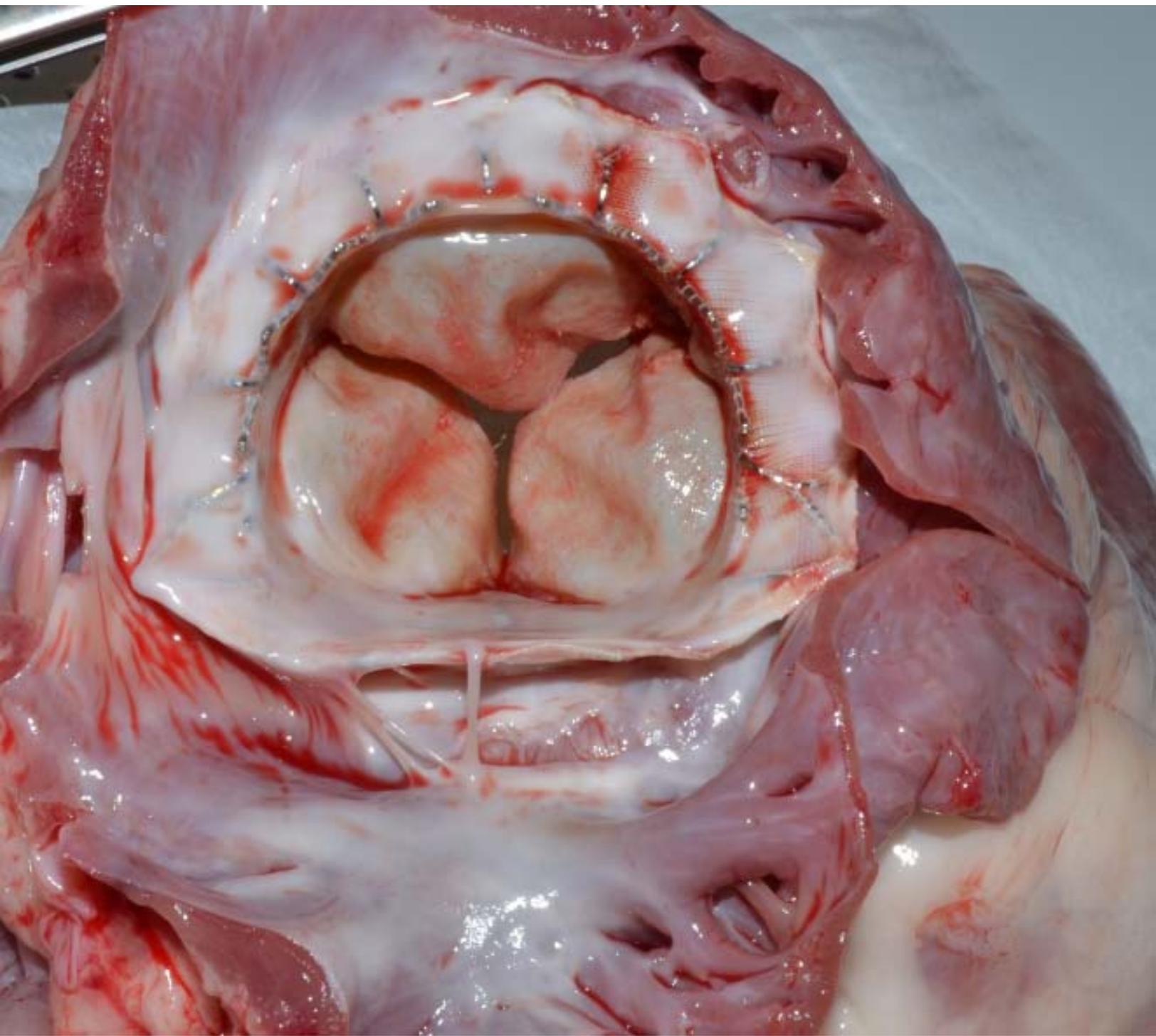












aortic-mitral  
curtain

Atrial  
"skirt"

