Title: Acute performance of a novel restorative transcatheter aortic valve: preclinical results.

Authors: Yosuke Miyazaki, M.D, PhD; Osama I. Soliman, M.D, PhD; Mohammad Abdelghani, M.D, MSc; Athanasios Katsikis, M.D, PhD; Christophe Naz, MSc; Susana Lopes, MSc; Boris Warnack, PhD; Martijn Cox, PhD; Yoshinobu Onuma, M.D, PhD; Patrick W. Serruys, M.D, PhD

DOI: 10.4244/EIJ-D-17-00554


Guest Editor: Alec Vahanian, M.D

Manuscript submission date: 29 June 2017

Revisions received: 25 September 2017

Accepted date: 20 October 2017

Online publication date: 24 October 2017

Disclaimer: This is a PDF file of a "Just accepted article". This PDF has been published online early without copy editing/typesetting as a service to the Journal's readership (having early access to this data). Copy editing/typesetting will commence shortly. Unforeseen errors may arise during the proofing process and as such Europa Digital & Publishing exercise their legal rights concerning these potential circumstances.
Acute performance of a novel restorative transcatheter aortic valve: preclinical results

Yosuke Miyazaki¹, MD, PhD; Osama I. Soliman¹,², MD, PhD; Mohammad Abdelghani³, MD, MSc; Athanasios Katsikis⁴, MD, PhD; Christophe Naz⁵, MSc; Susana Lopes⁵, MSc; Boris Warnack⁵, PhD; Martijn Cox⁵, PhD; Yoshinobu Onuma¹,², MD, PhD; Patrick W. Serruys⁶, MD, PhD

1. Department of Cardiology, Thoraxcenter, Erasmus Medical Center Rotterdam, Rotterdam, the Netherlands,
2. Cardialysis, Rotterdam, the Netherlands,
3. Department of Cardiology, the Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands,
4. 401 General Military Hospital of Athens, Cardiology department, Athens, Greece
5. Xeltis, Eindhoven, the Netherlands,
6. NHLI, Imperial College London, London, United Kingdom

Short running title

Preclinical results of restorative aortic valve

Address for correspondence:

Professor. Patrick W. Serruys, MD, PhD.

Imperial College London, London, The United Kingdom

P.O. Box 2125, 3000 CC Rotterdam, the Netherlands

Email: patrick.w.j.c.serruys@pwserruys.com
Keywords: TAVI, videodensitometry, Aortic stenosis, Imaging modalities, biodegradable; echocardiography; outcome

Number of figures: 5, Number of tables: 1, Total words 4970
Abstract

**Aim:** The XELTIS aortic valve leaflets are made from a bioabsorbable supramolecular polymer that guides the tissue to restoring itself. It is mounted on a self-expandable nitinol frame that includes three feelers and a native leaflet clipping mechanism. We sought to investigate the acute valve performance in a preclinical setting.

**Methods and results:** In 33 sheep, 26 mm XELTIS aortic valve were transapically implanted in a 23 mm native annulus. Aortography (analysable, n=28) and echocardiography (analysable, n=20) were acquired immediately after implantation of the XELTIS aortic valve to assess the acute device performance. On echocardiography, transvalvular peak pressure gradient (PG) was 7.4[IQR: 6.0-8.9] mmHg, mean PG was 4.0[IQR: 3.0-5.0] mmHg, and effective orifice area was 2.2[IQR: 1.6-2.5] cm². Trace(n=6) and mild(n=2) and no(n=12) transvalvular aortic regurgitation (AR) were seen. Likewise, no paravalvular AR was detected in 7 cases, whereas trace, mild and moderate were seen in 7, 5 and 1 case, respectively. On quantitative Videodensitometric-AR (VD-AR) assessment, a median value of 6[IQR: 1-12]% of AR was seen. Three cases had a VD-AR superior to 17%, which has a prognostic significance. Out of these three cases 2 had echocardiographic assessment available, and showed mild and moderate paravalvular regurgitation, due to inadequate leaflets clipping.

**Conclusions:** In a transapical ovine model, the novel restorative transcatheter aortic valve with bioabsorbable leaflets demonstrated good hemodynamic performances comparable to commercially available devices. The highly porous polymeric leaflets demonstrated good competence immediately after implantation with no cases having >mild transvalvular AR.
Condensed abstract

XELTIS’ absorbable aortic valve guides functional restoration of natural tissue by endogenous tissue restoration (ETR). Hemodynamic and aortic regurgitation immediately after implantation of the XELTIS aortic valve (trans-apical TAVI) were analysed by echocardiography and aortography. Trans-valvular peak pressure gradient (PG) was 7.4 [6.0-8.9] mmHg, mean PG was 4.0 [3.0-5.0] mmHg, and effective orifice area was 2.2 [1.6-2.5] cm². Videodensitometric-AR, which provides quantified aortic regurgitation by aortography showed a median value of 6% [IQR: 1-12%]. A level of regurgitation comparable or inferior to those observed with commercially available bioprosthesis valves; a novel restorative transcatheter aortic valve demonstrated good hemodynamic performances with acceptable degree of regurgitation.
Abbreviation

TAVI: transcatheter aortic valve implantation

ETR: endogenous tissue restoration

VD-AR: Videodensitometric-aortic regurgitation

LV: left ventricle

ROI: region of interest

TDC: time density curve

AUC: area under the curve

PG: pressure gradient

LVOT: left ventricle outflow tract

VTI: velocity time integral

SD: standard deviation

IQR: interquartile range

PVR: paravalvular regurgitation

CMR: cardiovascular magnetic resonance
Introduction

Transcatheter Aortic Valve Implantation (TAVI) is an established treatment of aortic stenosis with expanding indications towards younger and lower risk patients. However, durability concerns emerge related to signals of an accelerated degeneration of transcatheter aortic valves leaflets, which represents the major barrier limiting TAVI expansion to new patients’ strata\(^1\)\(^-\)\(^2\). Current bioprosthetic valves are made of animal-derived glutaraldehyde-fixed foreign material, which raises several issues, such as durability, thromboembolism, infection, stenosis and regurgitation. Tissue of animal origin tends to degenerate and becomes calcified with time, so that in the span of a life time, re-intervention (re-operation) is frequent after one or two decades in the patient who received bio-prostheses implanted surgically or percutaneously\(^3\).

A restorative valve was developed based on a novel technology named “endogenous tissue restoration (ETR)”. The principle of ETR is that a leaflet of a bioabsorbable material will be progressively replaced by endogenous tissue\(^4\). As schematically shown in Figure 1, the implant is created by electrospinning a bioabsorbable polymer to form a three dimensional construct, such as a heart valve. The construct is implanted without adding any cells or growth factors, and is functional upon implantation. The porous microstructure of the implant allows cells to migrate into the construct, after which these cells start to produce neotissue that fills the pores and gradually takes over functionality from the gradually absorbing polymer. This new technology could potentially overcome the issues of the current available valves caused by the use of foreign material. Paediatric conduit (Fontan) and pulmonary valved conduit with this technology were investigated in-vitro, in preclinical setting and are currently tested in clinical setting\(^5\)\(^,\)\(^6\). With regard to the extension of this technology to aortic valve, this is the first report to investigate the acute performance of the XELTIS aortic valve.

Method

Study design

This preclinical study included 33 Ile de France sheep that received the XELTIS aortic valve by transapical approach. The first seven sheep were used for iterative design optimizations after which 26 sheep were implanted the XELTIS aortic valve. This study reports the acute performance of the XELTIS aortic valve implanted in these 33 sheep. Post implantation aortography was performed at the end of procedure to evaluate
the acute performance of the valve. Echocardiography was obtained after procedure. The study was conducted in compliance with ISO 10993-2. The Animal Care and Use Committee of the testing facility is registered at the CNREEA under the Ethics Committee n° 37.

Design of the XELTIS aortic valve and implantation of the XELTIS aortic valve

The XELTIS aortic valve (Xeltis BV, Eindhoven, the Netherlands) is made from a bioabsorbable supramolecular polymer. More specifically, polyester-urethanes were used that contained the ureidopyrimidinone (UPy) supramolecular binding motif. A key attribute of this class of materials is that mechanical properties and absorption characteristics can be changed and tuned independently, thus allowing selection of the appropriate material configuration through a process of elimination and optimization. Three polymer configurations were used to construct the XELTIS aortic valve in this study. The supramolecular polymers were used to synthesize the leaflets (through an electrospinning process) and the leaflets were mounted on a self-expandable nitinol frame that included three feelers and a native leaflet clipping mechanism. Extremities of the feelers were encapsulated with bioabsorbable materials to avoid damage to the leaflet as seen in the first series of seven implants (Figure 1).

Implantation procedure of the XELTIS aortic valve

All procedures were performed under general anaesthesia. The XELTIS aortic valves were implanted by a transapical approach under the guidance of echocardiography, fluoroscopy and aortography. A pigtail catheter is introduced transfemorally and placed in the native aortic valve cusp as reference for positioning. The valve is delivered transapically using fluoroscopy guidance. The distal end of the valve is deployed first after which the delivery system is pulled gently to anchor the 3 device arms into the sinuses of valsalva, prior to full deployment and release of the device (Figure 2).

Quantification of aortic regurgitation assessment by aortography using video-densitometric technology

Videodensitometric-AR (VD-AR) was analysed at an independent core laboratory (Cardialysis Clinical Trials Management and Core Laboratories, Rotterdam, the Netherlands) by experienced observers who were blinded.
to echocardiogram results. A dedicated software (CAAS A-Valve 2.0.2; Pie Medical Imaging, Maastricht, The Netherlands) was used to quantify the regurgitation from angiograms. The details of this technique have been described elsewhere\textsuperscript{8-14}. After delineating the aortic root (i.e. reference area) and the subaortic one third of the left ventricle (i.e. region of interest [ROI]), the contrast time-density curves (TDCs) are analysed both in the ROI (in the LV) and the reference region (the aortic root) during at least three cardiac cycles after contrast injection. The area under the curve (AUC) is automatically calculated and represent time-density integrals. VD-AR is automatically calculated as the ratio of the AUC of the time-density integrals measured in the ROI and the reference area. Theoretically, the value of VD-AR ranges from 0 to 1 (Figure 3).

**Aortic regurgitation and hemodynamic data assessment by echocardiography**

Echocardiographic data were analysed in accordance with the recommendations of the American Society of Echocardiography/European Association of Cardiovascular Imaging\textsuperscript{15-17}. Mean and peak pressure gradient (PG) across the XELTIS aortic valve were derived from continuous wave Doppler evaluation of blood flow in the left ventricle outflow tract (LVOT) and across the prosthetic device by manual tracing of the timed integration of the velocity curve. Aortic valve area was calculated by continuity equation using following measurements: 1) Velocity-time-integral (VTI) from LVOT level measured by pulsed-wave Doppler, 2) Velocity-time-integral (VTI) across aortic valve prosthesis level measured by continuous wave Doppler, and 3) diameter of the LVOT at the same location of pulsed-wave Doppler sample in the LVOT. For the assessment of aortic regurgitation (AR) severity and the origin of AR, Core Lab used a standard methodology as described earlier in several Core Lab publications\textsuperscript{18,20}.

**Statistics**

When continuous variables were normally distributed, we summarized data as mean ± standard deviation (SD). If they were not normally distributed, median and inter-quartile range [IQR] were used.
**Results**

Between April 25, 2016 and October 10, 2016, 33 devices with a diameter of 26 mm were implanted transapically in native annulus with an approximate diameter of 23 mm. Aortography was performed after implantation of the XELTIS aortic valve in all 33 sheep. In order to assess the acute device performance, echocardiography was performed immediately after the procedure in twenty consecutive cases after the initial and purely angiographic assessment of the first 13 cases.

**Procedural success**

Overall, there were no major complications in the majority of cases after TAVI procedure. However, two cases suffered from complications during the procedure because one of the feelers did not deploy well. Few cases showed issues in the subacute phase (>24hrs and <2 weeks), which were mainly related to 1) perforation of the native cusps due to improper coverage of the stent feelers and 2) abrasion of the mitral valve against the aortic valve stent frame resulting in mitral insufficiency. In most cases mitral valve abrasion was a consequence of stent migration due to perforation of the native cusps. Small improvements to the strut and frame protection were made during the study, which successfully eliminated these subacute issues.

**Quantification of aortic regurgitation after implantation of XELTIS aortic valve**

Aortic regurgitation (AR) after implantation of the XELTIS aortic valve was quantified by video-densitometric assessment. Five animals were not analysable due to the following reasons: 1) the ROI moved by deep breath (n=3) and 2) the ROI was not included in the aortography (n=2). Twenty-eight animals were analysable for this assessment. The median and IQR of VD-AR was 6%[1-12%] (figure 4). We compared the VD-AR in the first 7 iterative cases with the next 26 cases. There were 6 (86%) versus 22 (79%) analyzable cases for VD-AR in the first 7 cases and the next 26 sheep, respectively. Median [IQR] VD-AR was 8% [1.8-9.8%] versus 5.5% [1.0-14.0%] in the first 7 iterative cases and the next 26 sheep (p=0.89), respectively. Three cases showed a regurgitation superior to 17%, a value which is has a prognostic significance in clinical practice13.
Acute hemodynamic performance of the XELTIS aortic valve

Hemodynamic performance was assessed immediately after implantation of the XELTIS aortic valve in 20 cases. Trans-valvular peak pressure gradient (PG) was 7.4 [6.0-8.9] mmHg, mean PG was 4.0 [3.0-5.0] mmHg, and effective orifice area was 2.2 [1.6-2.5] cm². (Figure 5)

Severity of aortic regurgitation by echocardiography

Twenty cases were analysable for the severity of paravalvular regurgitation (PVR) and transvalvular regurgitation by echocardiography. Seven cases were observed without any PVR. Seven cases had trace, 5 cases mild and 1 case moderate PVR. In terms of transvalvular regurgitation, 12 cases had none, 6 cases trace and 2 cases mild transvalvular regurgitation. Out of the three cases with video-densitometric assessment superior to 17%, 2 had echocardiographic assessment available, and showed mild and moderate paravalvular regurgitation. These cases were attributed to a inappropriate clipping of the leaflets.

Discussion

The main findings of this study are as follows: 1) the XELTIS aortic valves were implanted safely via trans-apical approach, 2) hemodynamic performance immediately after implantation of the XELTIS aortic valve was excellent compared to the objective performance indices of the current commercially available bioprosthetic valves, 3) substantial regurgitation was observed in three cases, however those paravalvular regurgitation were due to the inadequate clipping of the leaflets and 4) otherwise, only less than mild tansvalvular regurgitation were observed.

Added value of the XELTIS aortic valve

TAVI was primarily introduced for treating elderly high-risk patients with severe aortic stenosis. Because of the limited life expectancy, there was a less focus on the long-term durability. However, patient selection of TAVI has been increasingly expanded to younger patients and/or lower surgical risk. Therefore, the long-term durability of TAVI prosthesis became important. Although most of the current available studies have not shown significant deterioration-related problems, longer term data in large cohorts is needed to conclude.
Current bioprosthetic valves are based on animal-derived glutaraldehyde-fixed pericardial tissue, which have known to lead the biocompatibility concerns due to chronic inflammatory responses. The chronic inflammation could lead to calcification through secretion of cytokines by macrophages, such as osteopontin. As clinical consequences, there is a need for adjunctive pharmacotherapy (long term aspirin therapy and short-term systemic anticoagulation) and repeat hospitalizations with or without re-interventions. ETR technology is based on the fact that a leaflet of a bioabsorbable material will be progressively replaced by endogenous tissue. Therefore, ETR could improve biocompatibility resulting in less leaflet thickening. In addition, less valve leaflet thrombosis and thus less need for antithrombotic therapy. Thus, this valve could potentially overcome the issues of the current available valves caused by the use of foreign material.

**Angiographic aortic regurgitation after implantation of the XELTIS aortic valve**

The leaflets of the XELTIS aortic valve are constructed by electrospinning, so that the leaflet has a porous texture due to the random assembly of microfibers (figure 1). Therefore, the concern that transvalvular (trans-leaflet) AR could be initially present, existed. In fact, in the large majority of cases the videodensitometry of the outflow tract just detected trace of contrast medium. During surgical reconstruction of RVOT in clinical cases, the surgical operator uses to witness oozing of the blood through the wall of the conduit, but almost instantaneously the hemostasis is achieved. Red cell, fibrin and protein get caught in the fiber network and render the leaflets competent and no longer permeable to the angiographic contrast medium.

**Echocardiographic aortic regurgitation after implantation of the XELTIS aortic valve**

More than mild transvalvular regurgitation was not observed by echocardiography. Although quantitative assessment of regurgitation by aortography indicated that 3 cases had a regurgitation superior to the critical level of 17%, AR of 2 of these cases by echocardiography was shown to originate from paravalvular leaks due to inadequate clipping of native leaflet.

**Comparison with current available bioprosthesis valves**

Spethmann et al. reported the hemodynamic performance after implantation of Edwards Sapien and Corevalve, and Soliman et al. reported the hemodynamic data after implantation of Lotus and Sapien based on echocardiogram (Table 1). The severity of AR after implantation of the XELTIS aortic valve quantified by videodensitometry using aortography was compared to that of current commercially available valves, which...
were assessed in the Brazilian TAVI registry. VD-AR of the XELTIS aortic valve (6% [1-12]) was less than that of Sapien XT (10% [5-14]) and Corevalve (13% [7-22]), and was similar with that of Lotus bioprosthesis valve (3% [1-7]) (unpublished data). Although the current study is performed in a preclinical setting, and compared to the hemodynamic parameters reported in a clinical setting, the acute hemodynamic performance was excellent.

Limitations

First of all, although there was an attempt to make a large animal model with aortic stenosis, there are no well-standardized large animal models of aortic stenosis. Furthermore, while reasonable efforts should be made to mimic the human situation, it should be realized that there will always be differences between human and animal models. In our specific case, there were several challenges specific to the use of the sheep model that we were successful in solving. First, sheep have a very short aortic root, and therefore limited space for positioning the valve. In addition, the sheep aortic and mitral valve are very close to each other and reside in the same plane. These challenges might lead to an ill-positioned or too long aortic valve prosthesis, which may cause mitral valve damage because of abrasion against the aortic valve prosthesis. We were able to solve this by using a short design of the prosthesis and appropriate cushioning of parts that are at risk of causing abrasion. Another challenge relates to the absence of stenosis and calcification, which means that the sheep aortic valve cusps are very thin and fragile, compared to human aortic valve cusps, which are typically thick and calcified in cases of severe aortic stenosis. Since, the position of our valve is based on feelers that sit on the native cusps, further cushioning was required to avoid perforation of these thin native cusps by the feelers. For the purpose of assessing the XELTIS aortic valve leaflets, a reasonable effort in developing and optimizing the ovine model have been done. However, taking into account that the usage of normal animal for the current experiments, the acute performance of XELTIS aortic valve could be different in between non-aortic stenosis recipient and aortic stenosis recipient, suggesting further investigations are needed for the confirmation.

Conclusion

In a transapical ovine model, the novel transcatheter aortic valve with restorative leaflets demonstrated good hemodynamic performance. The hemodynamics of the valve is comparable to the commercially available valves implanted in clinical cases. The highly porous polymeric leaflets demonstrated very good competence immediately after implantation with no cases having a more than mild transvalvular AR.
Figure legends

Figure 1. The principle of electrospinning and ETR of the XELTIS aortic valve

A) The principle of electrospinning: Electrospinning is a widely used technique for the electrostatic production of nanofibers, during which electric power is used to make polymer fibers with diameters ranging from 2 nm to several micrometres from polymer solutions or melts. This process is a major focus of attention because of its versatility and ability to continuously produce fibers on a scale of nanometres, which is difficult to achieve using other standard technologies. Electrospinning is a relatively simple way of creating nanofiber materials, but there are several parameters that can significantly influence the formation and structure of produced nanofibers. These parameters such as solution variables, needle variables or collector variables could be manipulated to produce the desired material.

B) Electron microscopic images of the product of electrospinning.

Reproduce and adopted with permission from Leo A. Bockeria et al. ⁵

C) Leaflets with a porous microstructure made through electrospinning process were mounted on a self-expandable nitinol frame that included three feelers and a native leaflet clipping mechanism.

D) The principle of ETR: The XELTIS aortic valve is gradually infiltrated by blood elements (red cells, platelets, macrophages), myoblasts, fibroblasts with subsequent enzymatic bioabsorption of the fibers, and gradually replaced by endogenous tissue.

Figure 2. Implantation of the XELTIS aortic valve

Figure 3. Videodensitometric assessment of aortic regurgitation

A) Delineation of the aortic root (reference area: red area in the aortography) and the subaortic one third of LV (ROI: yellow area in the aortography) are shown by the analyzer. B) The time density curves are provided for both the ROI (yellow TDC) and the reference region (red TDC) and the AUC is automatically computed by the software time-density integrals. VD-AR corresponds to the relative AUC, which is automatically calculated as the ratio of the relative AUC (ROI [yellow] and reference area [red]). Theoretically, the value of VD-AR ranges from 0 to 1.
Reproduce and adopted from Tateishi et al. EuroIntervention 2016

Figure 4. Cumulative frequency distribution curves of quantitative aortic regurgitation assessment (VD-AR) after implantation of the XELTIS aortic valve by videodensitometry
Cumulative frequency and median value of VD-AR immediately after implantation of the XELTIS aortic valve was shown.

Figure 5. Hemodynamic performance after implantation of the XELTIS aortic valve
Cumulative frequency and median value of A) peak pressure gradient across the valve, B) mean pressure gradient across the valve and C) effective orifice area immediately after implantation of the XELTIS aortic valve were shown.
Impact on daily practice (in no more than 3 sentences)

Current study showed that the acute results of the XELTIS aortic valve were good in a preclinical setting. Although long term results should be investigated, restorative valve could have the potential to overcome the issues of current commercially available bioprosthetic valves.

Conflict of interest

Christophe Naz, Susana Lopes, Boris Warnack and Martijn Cox are employed by Xeltis.
Table 1. Comparison of hemodynamic data between current commercially available valve and XELTIS aortic valve

<table>
<thead>
<tr>
<th></th>
<th>Human data from clinical trial</th>
<th>Preclinical data from normal sheep</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Edwards Sapien (26mm)²⁹</td>
<td>CoreValve (26mm)²⁹</td>
</tr>
<tr>
<td>Peak pressure gradient</td>
<td>15.8</td>
<td>15.5</td>
</tr>
<tr>
<td>Mean pressure gradient</td>
<td>8.5</td>
<td>8.4</td>
</tr>
<tr>
<td>THV EOA (cm²)</td>
<td>1.82</td>
<td>1.78</td>
</tr>
</tbody>
</table>

Disclaimer: As a public service to our readership, this article -- peer reviewed by the Editors of EuroIntervention - has been published immediately upon acceptance as it was received. The content of this article is the sole responsibility of the authors, and not that of the journal.

Copyright EuroIntervention
Reference


Disclaimer: As a public service to our readership, this article – peer reviewed by the Editors of EuroIntervention – has been published immediately upon acceptance as it was received. The content of this article is the sole responsibility of the authors, and not that of the journal.


Figure 2
Figure 2.