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# A new apical closure device for full-percutaneous transapical heart valve procedures: in-vivo stress-tests

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# Acknowledgments

# List of abbreviations

**AV**: Aortic valve

**AS**: Aortic stenosis

**LF/LGAS**: Low flow/low gradient aortic stenosis

**TAVI**: Transcatheter aortic valve implantation

**TAVR**: Transcatheter aortic valve replacement

**SAVR**: Surgical aortic valve replacement

**TA-TAVI**: Transapical transcatheter aortic valve implantation

**TA-TAVR**: Transapical transcatheter aortic valve replacement

**TF-TAVI**: Transfemoral transcatheter aortic valve implantation

**TF-TAVR**: Transfemoral transcatheter aortic valve replacement

**TA-TMVR**: Transapical transcatheter mitral valve replacement

**BP**: Blood pressure

**CVP**: Central venous pressure

**ACT**: Activated clotting time

**HR**: Heart rate

**bpm**: Beats pro minute

**SBP**: Systolic blood pressure

**MAP**: Mean arterial pressure

**THV**: Transacatheter heart valve

# Abstract

**Background:** Aortic stenosis (AS) is the most common valve disease in adults and, worldwide, represents the third cause of cardiovascular disease, preceded by arterial hypertension and coronary artery disease (1). In developed countries the most common etiology of AS is age-related calcific disease. Symptoms of AS are dyspnea, (pre)-syncope and angina (2). For patients with symptomatic and/or severe AS, valve replacement represents the standard and definitive treatment (3). However, elderly patients with severe AS, frequently have relevant comorbidities which preclude a surgical approach for high surgical risk (4). Transcatheter aortic valve replacement (TAVI) is a valid alternative for these inoperable patients(5). At present transapical TAVI (TA-TAVI) is performed through a mini-thoracotomy. New devices need to be developed in order to aspire to less invasive, full-percutaneous procedures for TA-TAVI. Access and, especially, closure of the heart apex remain a challenge in a minimal invasive setting.

**Objectives and Methods:** The new occluder from Comed (Comed, Bolsward, The Netherlands) was designed to allow full-percutaneous performance of TA-TAVI. It consists in an auto-expandible device for left ventricular apical closure, made of woven Nitinol wires designed in two self-expandable round retention disks with a connecting extendable waist. In our study the device was implanted in five young pigs. In a first phase the device was studied under standard conditions and in a second phase we tested it under stress conditions with growing doses of intravenous adrenaline.

**Results:** Five plugs were introduced and deployed in five pig hearts with immediate good apical sealing. During phase 1 only traces of blood were collected (mean of 4±5ml of blood lost per animal), hemodynamic parameters remained stable and no plug dislodgement was observed. During Phase 2, mean systolic and diastolic peak levels reached 268±24mmHg and 175±17mmHg, respectively, without plug dislodgment or bleeding. Macroscopic post-mortem analysis of the hearts showed good fixation of the device without myocardial damages.

**Conclusions:** Our experience with the apical occluder showed good early results under standard conditions as well as under stress conditions. No major bleeding nor device dislocation or embolization was observed and there was no macroscopic myocardial structural damage. The good sealing properties of the plug in its final design also under hemodynamic stress-tests in our animal model gives additional integrity to this emerging access and closure variety for TA-TAVI. To assess the thrombogenicity risk of the inner-disk, supplementary chronic animal studies need to be performed.

**Keywords:** Transcatheter valve replacement; Transapical valve replacement; Apical closure device; Percutaneous heart valve procedures

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# Introduction and background

The aortic valve (AV) is a semilunar valve that performs a key role in the outflow of oxygen-rich blood from the left ventricular chamber. Under normal conditions the AV has three cusps (or leaflets): left coronary, right coronary and noncoronary cusp.

A bicuspid AV is found in 0.46% to 1.37% of the population, and represents the most common congenital heart defect (6).

Aortic stenosis (AS) is the narrowing of the aortic valve opening area, a condition restricting the outflow of oxygen-rich blood from the heart to the body. Other less common etiologies of left ventricular ejection obstruction are subvalvular and supravalvular diseases. AS is the most common valve disease in adults and, worldwide, represents the third cause of cardiovascular disease, preceded by arterial hypertension and coronary artery disease



**Fig. 1 Illustration of the valvular apparatus**
The AV is situated centrally at the base of the heart. It consists of three semilunar cusps and the fibrous aortic annulus to which the cusps are attached.
*(Figure from: http://clinicalgate.com/surgery-for-acquired-cardiac-disease/).*



**Fig. 2 Representation of a normal aortic valve:** semilunar valve, composed of three leaflets and with an effective opening area measuring between 3 and 4 cm$^2$.
*Figure from: http://www.slideshare.net/*

(1). AS is a complex, multifaceted disease, and for severity assessment, different criteria are considered. The anatomy of the valve, its hemodynamic profile, the resulting left ventricular function and the symptoms related to the condition have to be studied. A normal AV opening orifice measures between 3.0 and 4.0 cm$^2$ (7). Generally, in AS we have a substantial diminution of AV opening area, accompanied by an increase of transvalvular gradient and an increase of maximal transvalvular jet-velocity. We talk about severe stenosis if there is an AV opening area < 1.0 cm$^2$, a mean transvalvular gradient > 40 mmHg and/or a peak flow velocity > 4.0 m/s (8). In some situations, as AS worsens the left ventricle begins to fail and the ejection fraction declines to the point where there is a transvalvular gradient that, despite very small aortic valve area, remains low. This condition is called low flow/low gradient aortic stenosis (LF/LGAS). In LF/LGAS the low gradient may "mask" a serious condition (8). It's erroneous to say that in AS there is constantly high transvalvular gradient.

The three primary etiologies of AS are: calcific disease of a trileaflet valve, congenital abnormalities of the aortic valve (unicuspid or bicuspid AV) with superimposed calcification and rheumatic valve disease. In developed countries, the most common etiology of AS is
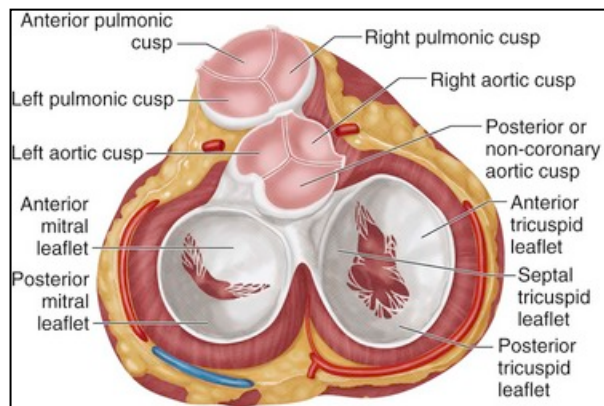
age-related calcific disease, a condition related to atherosclerosis and its risk factors (2). Such risk factors include, among others: older age, hypercholesterolemia, hypertension, smoking, diabetes and male sex (1). In the predisposition to calcific AS there is interplay of genetic, environmental and bio-cellular factors. The pathogenesis of calcific AS is composed of three key processes: lipid accumulation, inflammation
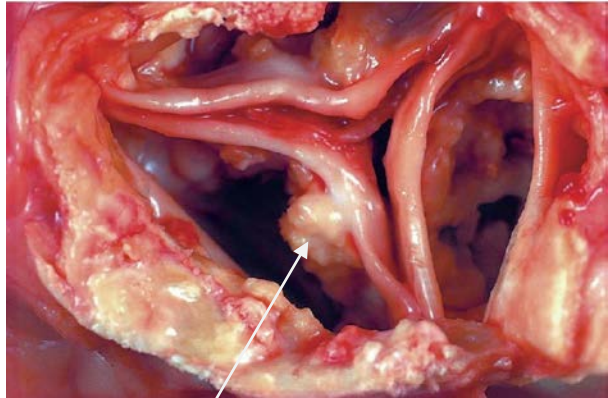


**Fig. 3 Calcific aortic stenosis**
Arrow: calcification
*(Figure from: https://www.studyblue.com/).*

and calcification. Calcific AS is a persistent condition with insidious progression (1).

As we enounced before, besides age-related calcific disease, other main etiologies of AS are congenital anomalies and rheumatic fever. The mainly described congenital anomalies leading to AS are unicuspid and bicuspid aortic valve, with superimposed calcification of the leaflet(s). The most common congenital cause of AS is bicuspid aortic valve, which most frequently results from a fusion of the left coronary and the right coronary leaflets during embryogenesis. Patients with a bicuspid valve have more susceptibility to degenerative alterations, AS and aortic insufficiency (or regurgitation) (1).
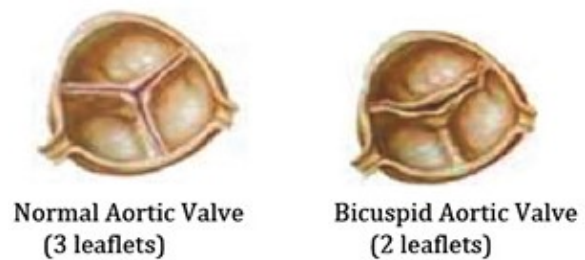


**Fig. 4 Normal tricuspid AV (left), bicuspid AV (right)**
On the right we can see the commonest type of bicuspid aortic valve, composed of:
- fusion of left coronary with right coronary leaflet
- posterior (non-coronary) leaflet.
*(Figure from: http://www.centralsydneycardiology.com/).*

Furthermore, it may be a site at risk for infective endocarditis. Bicuspid aortic valve is more frequent in males than in females and often remains silent early in life (9). Typically, bicuspid aortic valve is a sporadic condition, but it can also be part of a dominant autosomal disease with incomplete penetrance and may be part of an underlying thoracic aortic aneurysm syndrome. At present we should consider bicuspid aortic valve more as a complex cluster of diseases than as a unique disease, as it may have different morphological patterns, prognosis, complications and predisposing factors (10).

The third of the primary etiologies of AS is acute rheumatic fever, which has become very rare today in developed countries (1). Acute rheumatic fever appears two to four weeks after a group A *Streptocuccus* pharyngitis, and its major manifestations are: arthritis, pancarditis (pericarditis, myocarditis and endocarditis), central nervous system involvement (e.g. Sydenham chorea), erythema marginatum and subcutaneous nodules (11).

Rheumatic valve disease is a condition leading to the fusion of the leaflets' commissures and consequently to the narrowing of the valve opening area (12). Commonly rheumatic disease

affects the mitral valve first, this is the reason why rheumatic aortic valve disease is almost constantly associated with mitral valve stenosis and/or regurgitation (1,12).

Other less common causes of AS are systemic lupus erythematosus, metabolic diseases such as Fabry's disease and alkaptonuria. In patients with end-stage renal disease or Paget's disease, calcific AS may develop earlier in time and may progress quicker. Worldwide the main cause of AS is rheumatic fever, due to its high incidence in underdeveloped countries, whereas in more



**Fig. 5 Some of the mainly described manifestations of acute rheumatic fever**
Subcutaneous nodules - Sydenham chorea - Arthritis - Mitral valve calcifications - Skin rash
*(Figures from: http://intranet.tdmu.edu.ua/).*

developed countries such as Europe and North America main etiologies for AS are calcific disease and congenital abnormalities (12).

Concerning the evolving epidemiology of AS, a population-based prospective study has shown that prevalence increases exponentially with age (13). According to a report published by the United Nations in 2015, we can expect an important augmentation of the population of the elderly in the next years (14). If we consider these two observations simultaneously, we can presume that we have to expect an augmentation of cases of patients with AS in the next years. The development of new techniques to improve efficiency and safety of the therapeutic options becomes therefore more challenging and of interest.

Like we mentioned before, in a normal, tricuspid aortic valve the effective opening area measures between 3 and 4 cm$^2$, which corresponds to the cross-section area of the left ventricle outflow tract. Antegrade blood flow velocity and valve gradient remain sufficiently unchanged until there is a narrowing of more than half of normal valve opening area (12).

Typically, as the stenosing process evolves, the left ventricle adapts itself with morphological changes in order to maintain its function preserved. The obstruction generated by AS results in increased left ventricular pressure, which subsequently leads to concentric hypertrophy to sustain wall strain. As AS progresses the left ventricle becomes less compliant and even with stable left ventricular size there is an increase in end-diastolic pressure (12).

Usually there is a prolonged asymptomatic period before onset of symptoms during AS progression (12). In fact the human body is capable of many adapting mechanisms, that can also occur in AS and that leave the patients asymptomatic for a certain time. Unfortunately, there is no algorithm to predict the outcome of patients with this insidious condition; thus close, personalized and regular follow-up is very important.

Once AS becomes symptomatic, generally this becomes a condition with very poor prognosis for the patient, if left untreated. This fact increases the interest in developing new techniques: to gain efficacy and to allow larger subgroups a therapeutic option (12).

Symptoms of AS are nonspecific, thus it is important for the clinician to know them in order to recall this diagnosis, especially when facing a patient with risk factors for AS. Typical early symptoms of AS occur under physical exertion, that can be moderate motion, but also very mild activity. Symptoms include dyspnea, presyncope (exertion dizziness) or syncope and angina. End-stage symptoms can be resumed with heart failure, syncope and angina. It can be challenging, especially in patients with moderate degree of AS, to determine whether these nonspecific symptoms are imputable to AS or to other respiratory or cardiologic concomitant conditions. It is important to emphasize that even if symptoms are absent or only mild, but there is a severe degree of valve stenosis (i.e. AV opening area $< 1.0$ cm$^2$), immediate valve replacement should be considered, since there is a serious risk of sudden death (7).

During physical examination, heart auscultation remains very important, in particular for early diagnosis in asymptomatic patients (15). AS should be evoked if there is a systolic murmur localized at the right, second intercostal space, parasternal and irradiating to the carotids.

The murmur of AS typically has a crescendo-decrescendo configuration, which reflects the change in systolic pressure gradient between left ventricular chamber and ascending aorta as ejection occurs. The intensity of AS murmur depends directly on cardiac output. A softer murmur may be present in the setting of heart failure and in presence of low cardiac output. Consequently, there is no direct correlation between murmur intensity and severity of the condition and we cannot establish the grade of AS basing ourselves on auscultation only. Nevertheless, auscultation remains an important step in the diagnostic procedure, especially in asymptomatic patients (15). In some cases the systolic murmur of AS may be very distinct, acoustically pure and high pitched at the apex, this phenomenon is called the «Gallavardin effect». If there is this transmission of the AS murmur to the apex, AS may be misinterpreted as mitral regurgitation (which also produces a systolic murmur) (9).
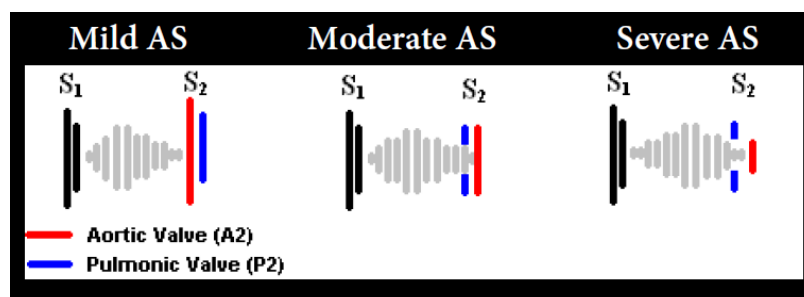


**Fig. 6 AS murmur: midsystolic, high pitched, crescendo-decrescendo ("diamond shaped").** Murmur in severe AS peaks later in systole because it takes longer for blood to eject through the valve. With worsening of AS intensity of S2 declines, there is a paradoxical split of S2 and a delayed aortic valve closure.
*Figure from:*
*http://www.healio.com/cardiology/learn-the-heart/cardiology-review/heart-murmurs*

Assessment of the carotid pulse can also provide some information. In AS a small and delayed upstroke pulse (*parvus* et *tardus*) is suggestive for severe disease. Nevertheless, carotid pulse examination is not always reliable, especially in elderly patients with concomitant stiffened, calcific arteries (9).

In the general evaluation of AS an electrocardiogram is also performed. AS doesn't have specific electrocardiographic patterns, although electrocardiogram is useful to monitor possible concomitant conditions like atrial fibrillation, left ventricular hypertrophy and signs of ischemia (7). In general, left ventricular hypertrophy (LVH) develops in relation to stenosis progression (9) and in some cases can be detected with chest radiography (as shown in figure 7) or with echocardiography.



**Fig. 7 Chest x-ray of a 48 years old patient with aortic stenosis and left ventricular hypertrophy (cardio-thoracic ratio > 50%).**
*Figure from: https://amboss.miamed.de/*

AS and systemic hypertension are the main causes of left ventricular pressure overload. LVH takes months to years to develop and predisposes patients to major cardiovascular complications like congestive heart failure and arrhythmias. Electrocardiographic changes in LVH that may be observed are increased QRS voltage, increased QRS duration, left axis deviation, repolarization (ST-T) changes, and left atrial abnormalities. A criteria used in the electrocardiographic diagnosis of LVH is the Sokolow-Lyon index (sum of S wave in V1 and R wave in V5 or V6 ≥ 3.5 mV (35 mm) and/or R wave in aVL ≥ 1.1 mV (11 mm) (sometimes ≥ 1.3 mV [13 mm]) (16).



**Fig. 8 ECG signs of left ventricular hypertrophy**
S in V1 is 15mm, R in V5 is 26mm. The sum is ≥ 35 mm (3.5 mV) which corresponds to LVH according to the Sokolow-Lyon criteria.
*Figure from: http://en.ecgpedia.org/*

Sometimes AS is primarily detected during routine echocardiographic controls. It is important to underline that the patient may be fully asymptomatic at the moment of diagnosis, but this shall not preclude further controls and close follow-up. The diagnosis of AS is primarily established with transthoracic echocardiography, which is also the technique of choice for instrumental evaluation during patients' follow-up (7).
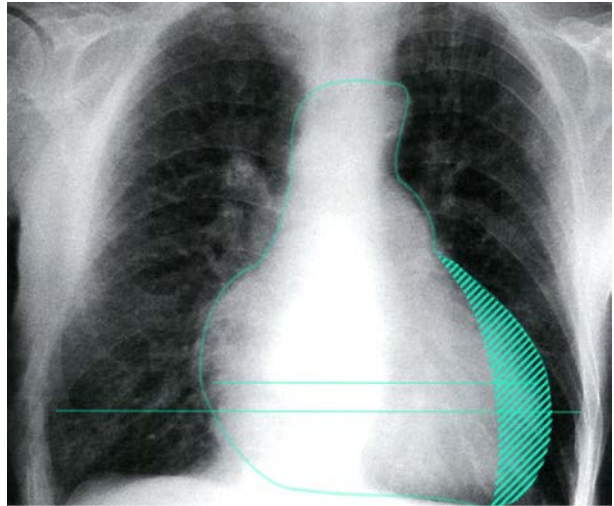
AS can lead to pulmonary artery hypertension as a complication, with severe pulmonary artery hypertension (systolic pressure > 50 mmHg) found in about 15% of patients with AS. This occurrence is explained by the progressive elevation of left ventricular diastolic pression during AS progression. In some cases it's difficult to determine whether pulmonary artery hypertension is imputable to AS or to other pulmonary comorbidities. Doppler echocardiography is an excellent technique to obtain an accurate, non-invasive



**Fig. 9 Five chamber echocardiographic view of a calcified aortic valve (stars) during diastole.**
*Figure from: https://www.uptodate.com/*

estimation of the pulmonary artery pressure and it is an important parameter to monitor during patients follow-up (7).

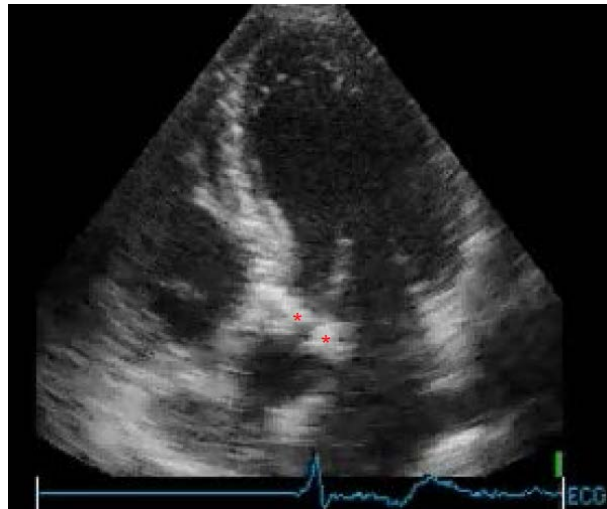Mitral regurgitation is also a common associated finding in AS (17), but is also common in other causes of left ventricular dysfunction, like in ischemic cardiomyopathy (18).

To resume this first introducing section we can say that AS is the most frequent native valvular disease in Europe (17), and that it's becoming a real public issue, as it has a poor prognosis if left untreated and there is an increment of cases in the last decades, which is consistent with the phenomenon of population ageing (19). AS is frequently found in elder, polymorbid patients (17), with high surgical risk.

For patients with symptomatic and/or severe AS (i.e. effective valve opening area < 1 cm$^2$, $V_{max}$ > 4 m/s), valve replacement represents the standard and definitive treatment (3). If patients' selection is accurate, peri-operative and long term outcomes of surgical aortic valve replacement (SAVR) in AS are very good (20). Besides SAVR and balloon aortic valvuloplasty, which is now rarely performed seen the unsatisfactory long term results (17), in the last years another technique is emerging: transcatheter aortic valve implantation (TAVI). The first TAVI was performed in 2002, since then it has become a large field of interest, development and research. At present TAVI is the treatment of choice for inoperable patients with indication for aortic valve replacement (21,22).

There are two main approaches for TAVI: transfermoral (TF-TAVI) and transapical (TA-TAVI). TA- and TF-TAVI are performed under general anaesthesia, in some cases the transfemoral access can be performed under loco-regional anaesthesia. It is recommended for the transapical access to prevent with fermoral accesses, in case of conversion to a surgical on-pump procedure (22).

Elderly patients with severe AS frequently have relevant comorbidities, which preclude a surgical approach for high surgical risk (4). Transcatheter aortic valve replacement is a valid alternative for inoperable patients (5).

The PARTNER study is a randomised trial that compares transcatheter aortic valve replacement (TAVR) to standard-of-care treatments in inoperable and respectively in high surgical risk patients with AS (23,24). The results of this randomized trial demonstrate that TAVR should be strongly recommended for patients
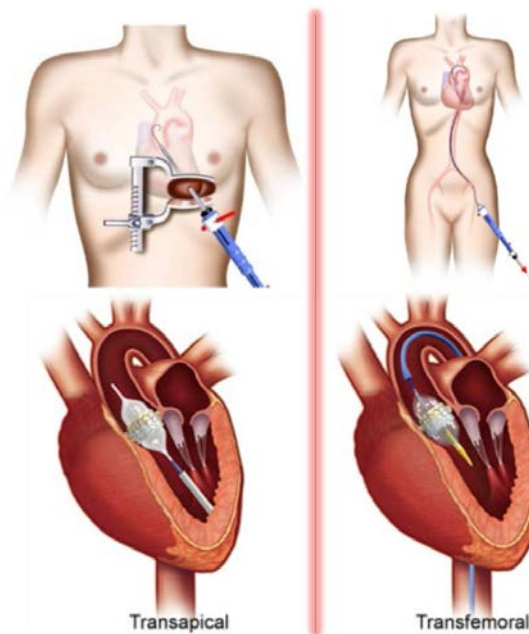


**Fig. 10 Illustration of TA-TAVI (antegrade through mini-thoracotomy approach) compared to TF-TAVI (transfemoral retrograde approach).** *Figures from: http://www.isarherzzentrum.de/ and http://oregon.providence.org/*

with severe AS and that cannot undergo surgery. In fact, in inoperable patient, TAVR provides longer survival and better functional status when compared to standard treatments (medical management with or without balloon aortic valvuloplasty) (23). Concerning patients with severe AS and high surgical risk, TAVR is as efficient as surgical aortic valve replacement (SAVR) in clinical outcomes and can therefore be recommended (24). This indications are based on 5-years of follow-up (23,24). Once it was demonstrated that TAVR is a valid therapeutic option for patients with high or prohibitive surgical risk, it was still unclear whether a transapical or a transfemoral approach had to be favoured. The PARTNER-I Trial substudy compares the transapical and the transfemoral approach for TAVR. The conclusions of this substudy are that we should primarily recommend the transfemoral access, because it provides better results in peri-procedural adverse events, less mortality and shorter recovery time when compared to the transapical access (25).

Even if the transfemoral access offers good results, it remains contra-indicated in some situations, for example in presence of too little vascular calibre, significant vessels tortuosity or atheroma. In these cases the transapical access is preferred for TAVR (26).

TA-TAVI is a minimally invasive, off-pump, beating heart technique for selected high risk patients requiring aortic valve replacement. It consists in an antegrade implantation adopting the oversizing technique with positioning of a stent based transcatheter xenograft, "crashing" and replacing the native diseased valve. For TA-TAVI femoral arterial and venous access wires are prepared (in case of conversion to an on-pump procedure), an anterolateral mini-thoracotomy is performed at the fifth or sixth intercostal space, apical purse string sutures or multiple reinforced U stiches are set up to prepare the left ventricle apex and an epicardial

pacing device is positioned for transient rapid ventricular pacing during valve positioning. Valve positioning is executed under fluoroscopic and echocardiographic guidance (27). In transapical access, fluoroscopy with coronary angiography allows visualization of the coronary anatomy and may contribute in lowering the risk of injury of the left anterior descending artery during puncture of the apex (28).

At present the standard introducer sheaths and delivery-catheters for transapical transcatheter aortic and mitral valve procedures have an outer diameter ranging from 22-Fr to 35-Fr. Preferably TA-TAVI is performed in a hybrid operative theater and by an experienced team of cardiac surgeons, cardiologists and anesthetists (27).

The first randomized multicenter study for TA-TAVI efficiency in high-risk patients, shows promising early results, with good peri-operative and post-operative hemodynamic results (29). Other studies show good early results of TA- and TF-TAVI in selected patients, nevertheless further studies are required to assess long term outcomes (30,31). Some other studies that investigate the outcome of TAVI, show only discrete results, with moderately high mortality rate in the year following the procedure (32,33). However, we must ponder these results with the high risk profile of the population eligible for this procedure, with general higher mortality. An encouraging observation is that no major decline in valve functioning was observed throughout the follow-up period of patients who underwent TAVI (33), meaning that the high mortality rate observed may not be correlated to the procedure itself.

Despite the advent of new low-profile introducer sheaths and new delivery catheters, the apical access still remains a challenge. The potential complications of TA-TAVI can rapidly turn into imminent life-threatening conditions; some of the main complications being: apical bleeding, stent-valve embolization, valve malpositioning, coronary obstruction, aortic root rupture and dissection, severe paravalvular leaks, infection, myocardial damage and ventricular tear (34).

As mentioned previously, TA-TAVI is currently performed with a left antero-lateral mini-thoracotomy at the level of the fifth or sixth intercostal space. Thoracotomies can be significantly invasive acts, especially for patients with relevant comorbidities (for example for patients with chronic obstructive pulmonary disease). Considering the fragile population eligible for TA-TAVI, we can presume that less invasive approaches could be very advantageous (27).

Our interest is to dispose of a device that allows less invasive access and closure of the left ventricular wall, in order to improve the TA-TAVI procedure, which has already shown promising results (30,31). The development of apical occluders for full percutaneous access is certainly an essential step towards minimal invasive TA-TAVI and for other transapical

procedures like transapical transcatheter mitral valve replacement (TA-TMVR). In this study we are going to discuss about a device designed and tested with this purpose.

# Objectives

During TA-TAVI procedures apical closure represents one of the most challenging and dangerous steps, as it is characterized by the risk for real major complications such as ventricular tear and massive bleeding. At present, TA-TAVI is performed with a left anterior mini-thoracotomy and the apex is traditionally prepared with two concentric purse-string sutures with reinforced 3-0 polypropylene.

Our objective is to evaluate the performance of a plug-device that has been conceived to allow a full-percutaneous approach of TA-TAVI. To do so, the device was implanted and then evaluated under stress conditions in five animals, in order to assess its sealing properties and its potential early complications under mechanical strain.

More in general, we aim to evaluate a strategy that may be profitable and efficient in the early future for the developing of less-invasive (full-percutaneous) transapical cardiac interventions.

# Methods I – Technical aspects

## *The apical occluder and its delivery system*

The occluder (fig. 11) from Comed (Comed, Bolsward, The Netherlands) was designed with the purpose of allowing full-percutaneous performance of TA-TAVI.

It consists of an auto-expandible device for left ventricular apical closure. It is made of woven Nitinol wires designed in two self-expandable round retention disks with a connecting extendable waist. The surfaces of the discs are slightly curved to better



**Fig. 11 The apical occluder in its final design.**

adapt with the ventricular wall anatomy. Inside the two disks there are two membranes of expanded Polytetrafluoroethylene (ePTFE) that guarantee at first a mechanical occlusion of the apical access sites and subsequently the blood clotting for acute and long-term haemostasis. The device is expected to occlude apical access sites ranging from a minimum diameter of 20-Fr to a maximum diameter of 35-Fr with four different sizes that will become available in the future.

## The 2-steps maneuver

The specific design allows a simple and user-friendly two-step maneuver for the deployment through large-size sheaths under fluoroscopic control (Figure 12).

Specifications for the device employed during our test are as follows: inner disk of 18mm diameter, outer disk of 16mm diameter, connecting extendable waist of 10mm diameter and 8mm long.
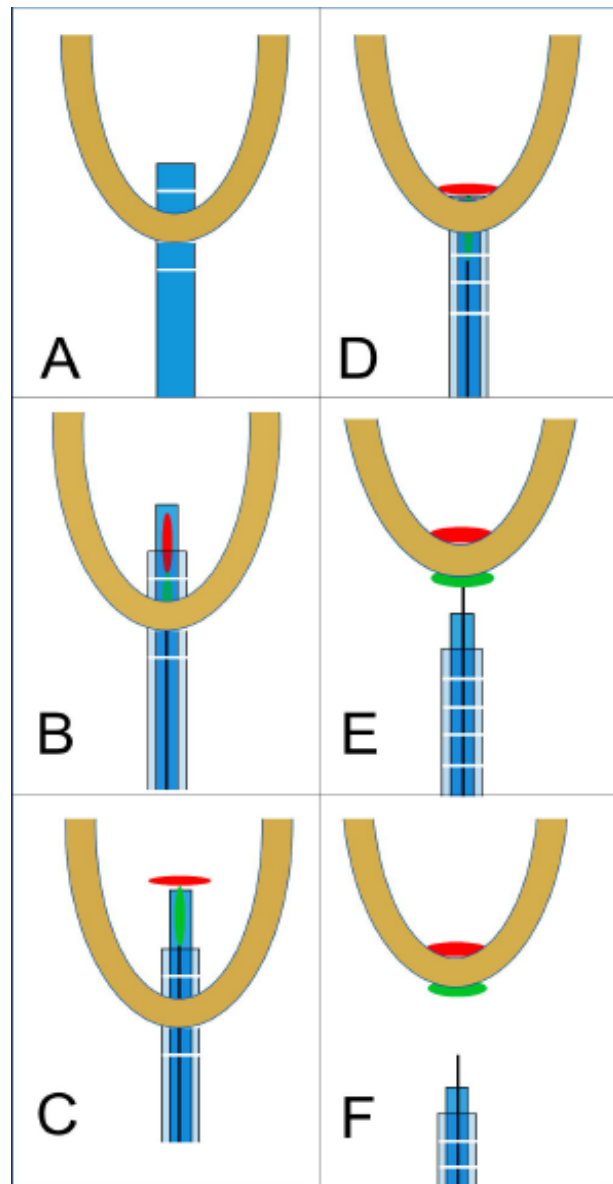


**Fig. 12 The two-steps maneuver for the deployment of the occluder.**

# Methods II – Study procedure

The plug device was implanted in five young pigs and subsequently a stress-test was performed to assess its sealing properties.

The procedures were performed in the animal laboratory of the Cardiovascular Research Unit, University Hospital of Lausanne, Switzerland.

Five young pigs (mean weight: 67±6Kg) received a premedication with Xylazine 0.1 mg/kg, Atropin 1 mg and Ketamine 10 mg/kg. For the induction of anesthesia we used a combination of Propofol and Isoflurane, orotracheal intubation was performed and successively we switched with Isoflurane 1.5-2.5% for the maintenance of sedation. After general anesthesia the animals received full heparinization (Liquemine by Roche, Switzerland: 100 UI/Kg; activated clotting time > 250 seconds).



Fig. 13 Apical plug device placed through a L-inverted sternotomy.

The accesses for drugs infusion, for invasive blood pressure (BP) monitoring, for central venous pressure (CVP) monitoring, and for blood sampling that we disposed where an arterial line (right common carotid artery) and a venous catheter (internal jugular vein). We monitored constantly electrocardiogram variations, BP, CVP, heart rate, and oxygen saturation (every 10 minutes during the standard hemodynamic conditions and every 5 minutes during the stress-test). After heparin and protamine administration, activated clotting time (ACT) measurements and gasometries were performed at baseline and 2 minutes after infusion. ACT was maintained above 250 seconds during wire and catheter insertion, during delivery of the occluder and during removal of the sheaths.

To proceed with the implantation and to assess the correct deployment and the cohesion of the apical occlusion device an inverted-L ministernotomy was performed. Through the inferior mini-sternotomies, 21-Fr introducer sheaths for transapical valve replacement (outer diameter: 25-Fr) were placed over-the-wire in the apexes,

Delivery-catheters carrying the occluders were inserted in the sheaths and subsequently the plugs were deployed under fluoroscopic guidance.

# Phase 1

In the first phase, following protamine sulphate infusion, blood was collected in the pericadium (for approximately one hour) under standard hemodynamic conditions. At the end of the first phase the pericardium was emptied completely and we proceeded with the second part of the study. Monitoring of hemodynamic parameters was performed every 10 minutes.

# Phase 2

In the second phase we induced systemic blood hypertension with adrenergic stimulation to test the sealing properties of the occluders under mechanical stress conditions. The animals have undergone the stress test for 30 minutes with growing doses of intravenous adrenaline (doubling of the dose every 5 minutes, sequentially 10, 20, 40, 80, 160, 320 mcg/minute).

We observed closely the holding of the devices under stress conditions as well as the hemodynamic response of the animal under catecholaminergic stimulation, the eventual bleeding events, thrombi formation or other complications.

At the end of the procedure the animals were sacrificed with intravenous propofol and hearts were analyzed macroscopically to evaluate the interaction of the device with the surrounding myocardium.

*The animals received care in conformity with the «Principles of Laboratory Animals» formulated by the National Society of Medical Research and the «Guide for the Care and Use of Laboratory Animals» prepared by the Institute of Laboratory Animal Resources and published by the National Institute of Health (NIH publication 85-23, revised 1985). The protocol was approved by the local Committee on Animal Research.*

# Results

The apical plug devices have been positioned successfully in the left ventricle apex of the five animals. Neither technical problems nor clinical complications occurred during the deployment maneuvers of the apical plug devices. Furthermore the devices showed excellent immediate holding property.

In Phase 1, under standard hemodynamic conditions, parameters were stable: heart rate (HR) at 87±14 beats pro minute (bpm) and mean arterial pressure (MAP) at 52±9 mmHg. During Phase 1, bleeding from sternum, mediastinum and heart was collected in the pericardium and measured at an average amount of 4±5 ml of blood loss per animal. The bleeding came mostly from the mediastinum and from the sternum. Mean hemoglobin values at baseline, after occluder deployment and at a the end of Phase 1 were 8.4±0.8 gr/dL, 8.2±0.6 gr/dL and 8.7±0.8 gr/dL, respectively.

Following the cumulative doses of intravenous adrenaline that we administered, we could observe a consistent increase of heart rate (graphic 1) and of systolic blood pressure (SBP) (graphic 2) in the five animals. The IV adrenaline stress-tests were performed over a period of time of about 30 minutes. During this stress-test we detected by hemodynamic monitoring maximal heart rate frequencies of 233±38 bpm, maximal systolic blood pressure values of 261±27 mmHg and maximal mean arterial pressure values of 203±23 mmHg.

During the entire procedure (apical occluder positioning and stress-test performance) we didn't succumb neither to important complications (like device dislocation or embolization), nor to major hemorrhagic events. The devices showed good holding properties also under conditions of relevant strain.

Post-mortem analysis of the hearts showed good fixation of the devices and no macroscopic myocardial damages.

Heart rate variation during stress-test

SBP variation during stress-test
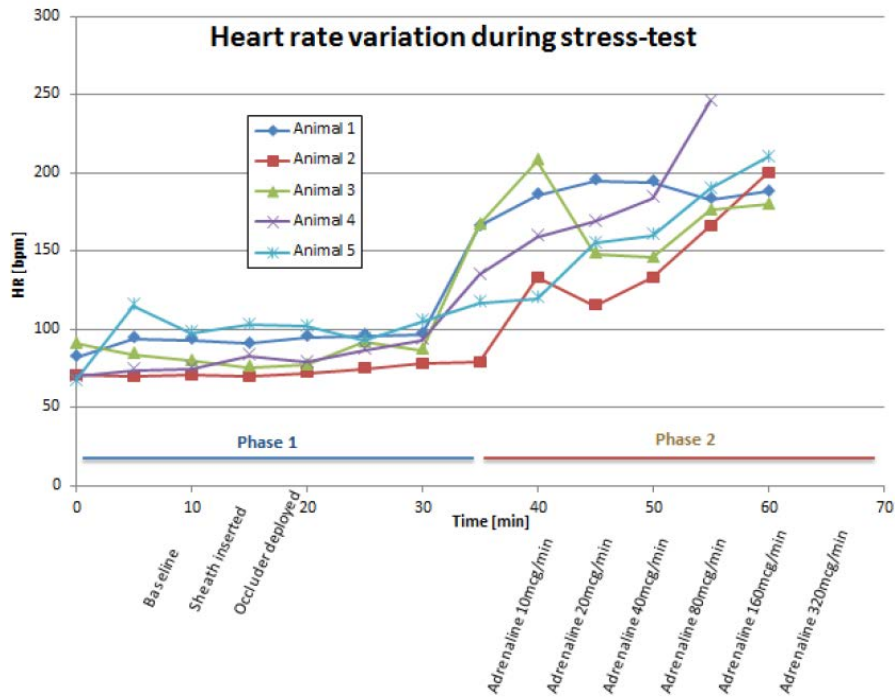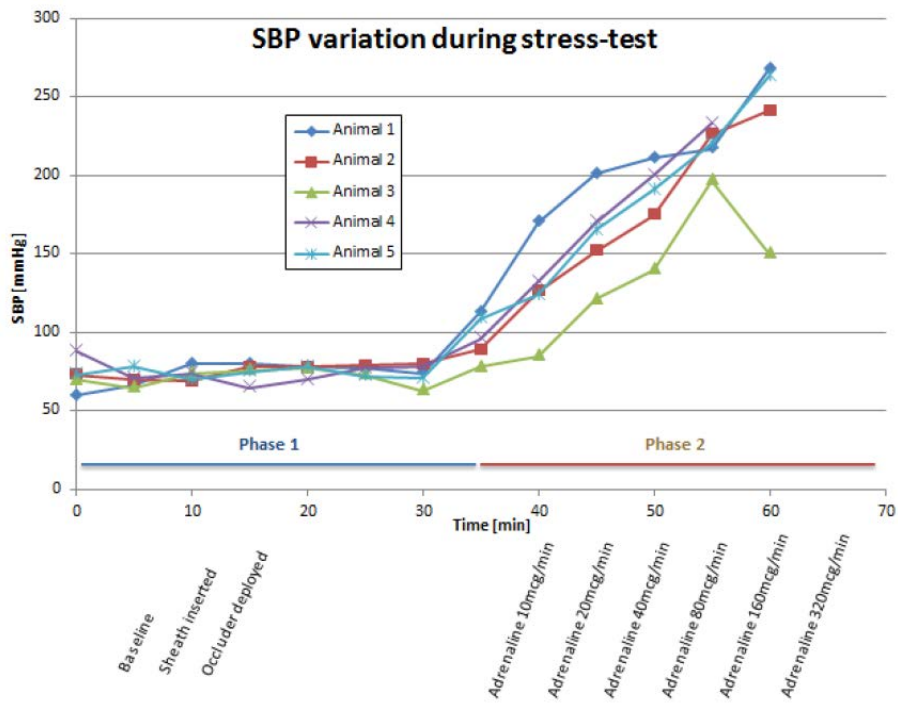
# Discussion

TAVI is a valid option for patients with severe AS and high or prohibitive surgical risk (23,24). Advanced age, left ventricular dysfunction and severe comorbid conditions are the main factors that preclude indication to surgery. An analogue situation happens with mitral valve disease, also having a growing prevalence concomitant to population aging, and for which innovative strategies (like the endovascular MitraClip system, since 2008) are gaining of interest, in order to offer less invasive procedures. It is interesting to underline that these new techniques are not replacing or stopping the continuous growth of surgical volumes, but they are becoming part of an integrated and multidisciplinary approach offering broader opportunities to the patients after accurate selection (35).

Transfemoral and transapical access are at present the standard access choices for TAVI. The transfemoral access has some contra-indications like severe peripheral artery disease. In these cases transapical access is preferred. Moreover transfemoral access requires a retrograde route, which despite the development of small calibre delivery systems, still represents a challenge and may generate shear stress in a diseased aorta or aortic arch (36). In comparison, the transapical access is characterized by the advantage of requiring a short course to the target site of the final interventional act, thus allowing a more precise deployment of stented valves (37). Furthermore, transapical procedures allow the access of large sheaths and consequently the introduction of biological valves and other devices of different nature in different sites (aortic and mitral).

However, at present the technology available to perform TA-TAVI with a mini-thoracotomy and with large delivery sheaths cannot allow full-percutaneous access or video-assisted thoracoscopic procedures. TA-TAVI still requires a mini-thoracotomy and is therefore still perceived as a more invasive procedure than TF-TAVI (37).

Percutaneous apical access route to the left ventricle is gaining of interest and is starting to be considered as a valid option in a certain number of cardiac procedures, such as closure of paravalvular leaks or atrial and ventricular septal defects. Transapical percutaneous access can provide a good, rapid and effective navigation in the left ventricle with shorter exposure-times to fluoroscopy and shorter procedural times when compared to the transfemoral/transseptal access route. Furthermore, transapical access can be advantageous if the patient has peripheral atherosclerotic vascular disease or hostile angles along the endovascular path.

With this study we aimed to determine whether the new apical occluder from Comed brings good short-time results and good sealing properties also under stress conditions.

After this study, we can conclude that the occluder shows very good sealing properties also under significant catecholamine-induced stress conditions. In fact, intravenous adrenaline

elicits a positive inotropic and chronotropic effect, enhances conduction in the heart system, induces relaxation of smooth muscle in the vasculature and bronchial tree and generates vasoconstriction. The onset of these hemodynamic effects by epinephrine infusion is dose dependent. We can consider that the doses we used in pigs were largely sufficient to enhance all of the mentioned effects, with a consequent high hemodynamic stress to the intraventricular disc of the apical occluder (38).

During the test, no major bleeding was observed and the implanted devices didn't engender macroscopic myocardial structural damage.

In the last years other studies described their experience with innovative devices designed to allow access and closure of the apex for TA-TAVI in the course of minimally invasive procedures (36,37,39,40). For example, in 2013 the first-in-man evaluation of the transapical APICA ASC™ system (Apica Cardiovascular, Galway, Ireland) (consisting of three parts: an introducer, a left ventricular low-profile titanium coil and a closure cap which is anchored and rotated into the myocardium almost like a corkscrew) was performed successfully in 10 patients (39). In another study TA-TAVI was performed with the APICA ASC™ device and second generation transacatheter heart valve (THV) in three elderly patients with successful hemodynamic outcomes, complete apical hemostasis and no peri-procedural major adverse events (40). Unfortunately, the APICA ASC™ device received CE-mark approval but was recently discontinued and, at present, the only available device approved for clinical use in Europe is the Permaseal™ (Micro International Device, PA, USA), which still requires a left antero-lateral mini-thoracotomy.

With the new self-expandable apical occluder we have the ambition to achieve a full percutaneous approach with large-size introducer sheaths, the repair of the ventricle after catheter withdrawal being one of the crucial steps after percutaneous TA-TAVI.

We already dispose of other previous experiences of devices and techniques tested for minimally invasive TA-TAVI. For example the use of the 12 mm Amplatz-nitinol occluder (AGA, Golden Valley, MN) in an animal study (a technique consisting of two square heads, squeezing and sealing the left ventricle apex) (41), the use of a supplementary pericardial patch sutured onto the ventricular head of the Amplatz-occluder  (to improve its sealing properties and reduce secondary bleeding) (42), minimally invasive apical procedures through umbilicus access in an animal study (43) and modified ventricular septal defect occluders for apical closure (44). We also reiterate our preliminary report on efficacy and safety of a prototype of the occluder device in an animal setting, with good results (37).

All of these experiences have shown encouraging results. Considering the technical improvement, the growing experience of the operators and the interest that will be engendered by this flourishing area of interest, we can expect a continuous development of this specific field in both aortic and mitral valve field. The good sealing properties of the plug

in its final design also during hemodynamic stress-test in our animal model give supplementary integrity to this potentially emerging approach variety for TA-TAVI.

However, some issues have still to be analyzed and addressed.

Concerning the traces of blood lost during this procedure we can predict that full-percutaneous transapical procedures in a clinical setting will require a small pericardial drainage placed percutaneously in order to evacuate the small amount of blood, which leaks mainly during sheath retrieval.

Concerning the thrombogenicity risk of the inner-disk, we still need to perform supplementary chronic animal studies. We can assume that there will be neo-endothelium formation on the surface of the inner-disk, and that probably there will be need of a three-month anticoagulation therapy or a double anti-platelet therapy to prevent thromboembolic events, as cardiologists traditionally do after the placement of atrial or ventricular septal defect occluders.

Limits of our pilot study are the acute animal setting, the limited number of animals (five) and the fact that the procedure was performed through a mini-thoracotomy and not yet in a full-percutaneous fashion.


## Conclusions

Our experience with the apical occluder showed good early results under standard conditions as well as under stress conditions. Neither major hemorrhagic events nor device dislocation and embolization were observed. Post-mortem macroscopic evaluation resulted negative for myocardial structural damage. The good sealing properties of the occluder under standard hemodynamic conditions as well as under catecholaminergic-induced stress conditions give additional integrity to this emerging access and closure variety for TA-TAVI.

This study may represent a step forward towards full-percutaneous transapical cardiac procedures.

We acknowledge the acute setting of our study. Chronic animal tests to evaluate the impact of the plug device on ventricular function, on potential rhythm disturbances and on thrombotic risk are already scheduled. The good results obtained here represent the point of departure and are certainly an important source of motivation for further progression in this specific and challenging field.

# Key words

Transcatheter valve replacement; Transapical valve replacement; Apical closure device; Percutaneous heart valve procedures

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