

Transcatheter Aortic Valve Implantation

Hans Henrik Møller Nielsen, MD, PhD

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Tutors: Vibeke Elisabeth Hjortdal & Leif Thuesen,

Official opponents: Andrew N. Redington, Canada & Truls Myrnes Norway

Correspondence: Department of Cardiothoracic Surgery, Aarhus University Hospital, Skejby, Brendstrupgårdsvej 100, 8200 Aarhus, Denmark

E-mail: hhm@kirurgi.org

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The 5 original papers are:

1. Nielsen HHM, Andersen HR, Hjortdal VE, Klaaborg KE, Jakobsen CJ, Egeblad H, Terp K, Lindskov C, Sloth E, Poulsen SH, Boing I, Thuesen L. [Catheter-based aortic valve substitution. Initial experiences with stent valve implantation]. *Ugeskr Laeger* 2009;171:2277-2281
2. Nielsen HHM, Egeblad H, Klaaborg KE, Hjortdal VE, Thuesen L. "Transatrial stent-valve implantation in a stenotic tricuspid valve bioprosthesis". *Ann Thorac Surg* 2011;91:e74-76.
3. Nielsen HHM, Thuesen L, Egeblad H, Poulsen SH, Klaaborg KE, Jakobsen CJ, Andersen HR, Hjortdal VE. "Single center experience with transcatheter aortic valve implantation using the Edwards SAPIEN Valve". *Scand Cardiovasc J* 2011.
4. Nielsen HHM, Egeblad H, Andersen HR, Thuesen L, Poulsen SH, Jakobsen CJ, Klaaborg KE, Hjortdal VE. "Aortic Regurgitation After Transcatheter Aortic Valve Implantation of the Edwards SAPIENTm Valve". [in preparation].
5. Nielsen HHM, Thuesen L, Hjortdal VE. "Nordic Study of Transapical Transcatheter Aortic Valve Implantation vs. Conventional Surgery – a Prospective Randomized Controlled Trial". [in preparation]

INTRODUCTION

Aortic valve stenosis

Aortic valve stenosis is the most common heart valve disease, affecting 2 % of the western population above 65 years[1]. Initial symptoms include dyspnoea and chest pain, whereas syncope and heart failure are signs of severe stenosis. Without treatment the patients suffer a grave prognosis, as the median survival following onset of symptoms is around 2 years[2].

Treatment modalities

The treatment strategy is decided from the severity of the stenosis and the patient's symptoms.

Medical treatment is recommended if the stenosis is moderate and the patient is asymptomatic. Surgery is considered in case of severe stenosis, with aortic valve area < 1 cm², or if the patient experiences symptoms related to the stenosis[3].

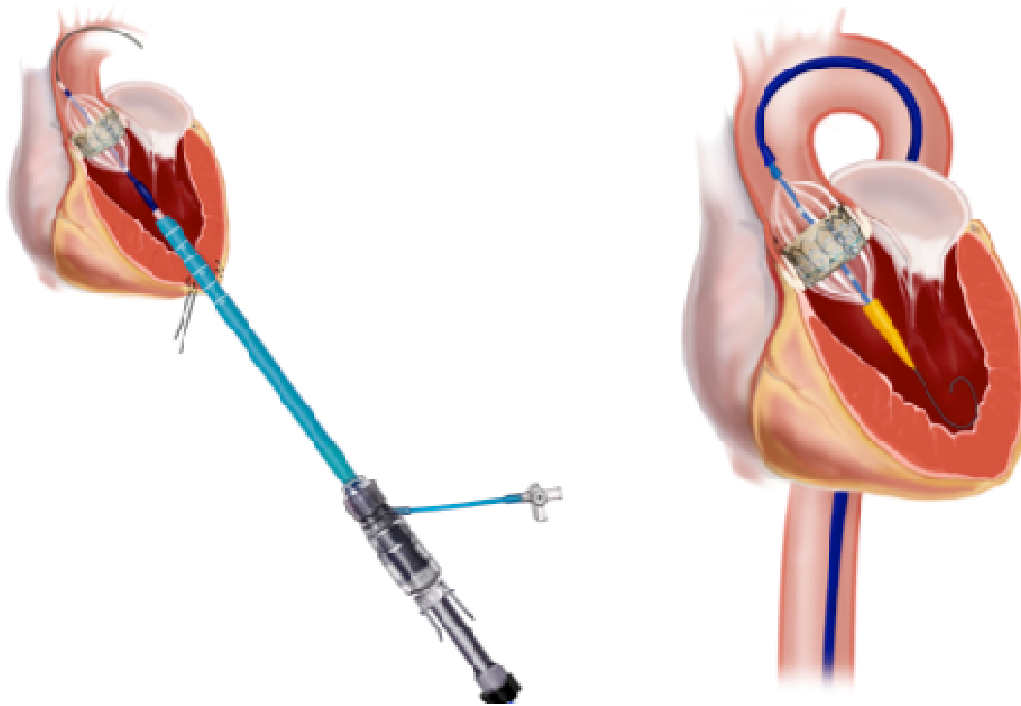
The standard operation is surgical aortic valve replacement (SAVR). This procedure is done through a sternotomy using cardiopulmonary bypass. After a successful valve implantation, the life expectancy is comparable to the general population[4]. In young patients with no co-morbidity, SAVR is a low risk procedure.

Advanced age and the existence of co-morbidity increase the procedure related risk, and reports suggest that up to one third of patients with aortic valve stenosis are denied surgery due to high-predicted risk[2, 5-7]. This fraction may be true when considering patients diagnosed with aortic valve stenosis among an entire population including the very elderly and even the moribund. However, the proportion of patients who are denied surgery is probably lower, when considering only referred patients with aortic valve stenosis and a relevant need and desire for invasive treatment. This may especially be true in the Scandinavian countries with free and equal access to medical care.

The first Transcatheter Heart Valve

In 1989 Henning Rud Andersen et al[8, 9] presented a radical new type of heart valve prosthesis. The prosthesis, later to be known as a transcatheter heart valve (THV), was initially named "The Stent-Valve". It had the properties of a stent, as it could be crimped on a balloon catheter and inserted transarterially without a sternotomy. This new procedure could potentially alleviate the surgical trauma associated with aortic valve replacement. After technical optimization and experiments in animals, Cribier et al. performed the first human implantation via a trans-septal antegrade approach in 2002[10]. In 2005, the retrograde approach via the femoral artery was introduced by John Webb, a much more feasible procedure. This approach was named femoral transcatheter aortic valve implantation (F-TAVI)[7, 11]. In 2006 Walther et al. introduced the apical transcatheter aortic valve implantation (A-TAVI) (Figure 1)[12]. The femoral and apical access routes, along with alternative arterial access sites, turned out to become a major therapeutic breakthrough for the TAVI procedure with a dramatic increase of implantations over the next years, adding up to over 40.000 implantations worldwide in 2011.[13]

Figure 1:



An illustration of the two different implantation routes. Apical transcatheter aortic valve implantation (left), and femoral transcatheter aortic valve implantation (right).
Image courtesy of Edwards Lifesciences

Valve Types

At present, two major valve companies have marketed clinically approved TAVI prostheses. The company Medtronic produces the CoreValve Revalving System® (Medtronic, Minneapolis, MN, USA), while Edwards Lifesciences produce the SAPIEN XT™ (Edwards Lifesciences, Irvine, CA, USA).

The CoreValve prosthesis is a self-expanding nitinol device, providing anchoring in both the left ventricular outflow tract (LVOT) and the supra-coronary aorta. The CoreValve prosthesis allows for gradual deployment and repositioning before release (Table 2). The balloon expandable Edwards SAPIEN valve, is considerably shorter than the CoreValve system and placed and anchored in the degenerated aortic valve annulus without possibility of repositioning (Table 2).

In registries, both prostheses are associated with similar procedural success rates and hemodynamic and clinical improvements. The difference in design results in an increased rate of atrio-ventricular block with need for pacemaker treatment after CoreValve implantations[14, 15].

Implantation technique

TAVI is performed in a cardiac catheterisation laboratory or hybrid suite, by a team of anaesthesiologists, cardiologists and - during A-TAVI - cardiac surgeons.

Before the procedure the patients complete a thorough examination program that normally includes:

- *Echocardiography*: transoesophageal echocardiography (TOE) and transthoracic echocardiography (TTE) to evaluate the severity of the stenosis, the left ventricular function and the diameter of the aortic annulus for valve sizing.

- *Electrocardiogram (ECG)*: to check for existing conduction disturbances, left ventricular hypertrophy or ischemia.
- *Coronary angiography (CAG)*: to determine any need for revascularization
- *Aorto- & Iliacography*: to measure the distance between the native valve and the coronary ostia along with the degree of valvular calcification. When planning femoral transcatheter aortic valve implantation (F-TAVI), iliac vessels are examined for tortuosity and acceptable vessel diameter.
- *Pulmonary function test (PFT)*: ventilation capacity is examined to determine if the patient will tolerate anaesthesia and mechanical ventilation.

The procedure technique differs slightly between the two approaches; A-TAVI and F-TAVI. (Figure 1)

A-TAVI

Transapical TAVI is performed using the Edwards SAPIEN XT™ valve and presently requires general anaesthesia, although epidural analgesia might be considered in the future. The apex of the heart is exposed through a left mini thoracotomy in the 4th intercostal space. Heparin is administered, and a guidewire is placed through the apex and crossing the aortic valve antegradely. Temporary myocardial pacing electrodes are placed superficially on the left ventricular surface, and a balloon dilatation catheter is advanced over the guidewire.

The native aortic valve is pre-dilated during rapid ventricular pacing (160-180 bpm). The stent-valve crimped on the balloon dilatation catheter is subsequently introduced and implanted during rapid pacing.[12, 16]

Placing of the valve is a crucial point during TAVI. Fluoroscopy and/or TOE are used for precise visualisation and placement of the prosthesis. The valve should be placed with one third of the stent height in the LVOT and two thirds above the annulus. Low placement increases the risk of embolization into the left ventricle and is thought to increase the risk of conduction disturbances[17], while high placement leads to risk of embolization into the aorta. The valve should be balloon dilated to fit the annulus with only slight oversizing, as too much oversizing may cause rupture of the aortic annulus. Valve performance is tested by aortography and TOE after implantation.

The A-TAVI approach benefits from the tolerance of larger catheter diameters compared to femoral TAVI (F-TAVI), hence allowing for larger and potentially more advanced valves. Furthermore, the apical approach can be used to reach the mitral valve.

F-TAVI

Femoral TAVI is associated with a smaller surgical trauma, as current generation F-TAVI catheters are down to 16F in size and can be inserted percutaneously. Both the Edwards SAPIENTm and the Medtronic CoreValve can be inserted via the femoral approach. This requires the femoral artery to be at least 6 mm in diameter[13].

The F-TAVI procedure is technically slightly more challenging, as the native valve must be crossed retrogradely. This, along with the longer working distance, makes the precise placement of the

distance from the leaflet hinges to the coronary ostia. Because of the increased leaflet size and risk of covering the coronary ostia, bicuspid valves are considered to be a relative contraindication for the procedure. Since the valve is only expanded against – and not sewn into the aortic annulus, there is an increased risk of paravalvular leakage [IV][22]. Furthermore, catheter implantable valves do not have a circular ring that keeps a constant shape of the prosthesis. This allows for potential deformation of the valve, which may lead to maladaptation of the leaflets and central regurgitation.

During TAVI, the valve is being manipulated against the atherosclerotic and calcified tissue inside the aorta, with a theoretical risk of releasing emboli into the bloodstream, causing ischemic lesions in the brain, kidney or intestine.

Complications

Conduction disturbances

Conduction disturbances requiring pacemaker implantation is seen in between 3-40 % of patients after TAVI, depending on centre, follow up time and THV type. Reports suggest that the pacemaker frequency is higher after CoreValve®- than Edwards SAPIENTm implantations (Table 1), when implanting larger THV sizes[14] and in patients with pre-existing right bundle branch block[23]. The severity and distribution of aortic valve calcification is however not an independent risk predictor[23].

Conduction disturbances during the TAVI procedures besides AV-block include: new onset of atrial fibrillation or ventricular fibrillation. Ventricular fibrillation may occur following rapid ventricular pacing or manipulation of the heart. Low LVEF is associated with a worse prognosis following TAVI.[24, 25]

Low LVEF is also a well-known risk factor in SAVR, where the mortality risk is greater in patients with left ventricular dilatation and/or low LVEF.[26-28].

valve prosthesis more difficult, especially when using THV systems without gradual deployment or retraction possibilities. Temporary pacing wires are placed transvenously. The native valve is pre-dilated during rapid ventricular pacing before the crimped THV is introduced and deployed by balloon dilatation (3-5 atmospheres pressure, depending on balloon size); or in the case of self-expanding CoreValve released by gradual removal of the covering sheath. F-TAVI may be performed during local anaesthesia.[7, 16, 18]

Valve-in-valve

The majority of catheter-implanted valves are inserted in the aortic or pulmonary position as replacement for the native valves. Another use of the technique is valve-in-valve procedures, where the valves are placed inside degenerated bioprostheses either via the apical or femoral approach[19]. This has been performed both in the aortic[20, 21], mitral and tricuspid [II] valve position with good results, although the resulting valvular opening area is limited by the internal diameter of the originally implanted prosthesis.

Limitations of the TAVI techniques and devices

Although associated with a smaller surgical trauma than SAVR, the TAVI procedure and the THVs have inherent limitations. Since the native aortic valve is left in place, the bulk of the calcified leaflets must fit within the aortic sinus, without compromising blood flow in the coronary arteries. This requires a certain

The increase in LVEF following treatment of aortic valve stenosis is a strong predictor of postoperative outcome.[26]

Aortic lesions

Aortic annulus rupture is a rare but feared complication caused by dilation of the THV, requiring acute surgical intervention[29, 30]. Rupture of the aortic annulus carry a poor prognosis, and may in some cases require reconstruction of the aortic root with the use of a homograft[31]. Whether annular rupture occurs as a consequence of high pressure in the expanding balloon and resulting over-dilatation of the THV, or because of decreased elasticity of the annulus due to excessive calcification, remains unknown.

Vascular injuries

Lesions of the abdominal aorta, femoral or iliac arteries, may occur during F-TAVI and may result in bleeding into the retroperitoneum, abdomen or thoracic cavity, leading to hypovolemia or ischemia. Vascular complications at the access site are reported in between 4-18% of cases[32-35]. While often requiring surgical repair and resulting in an increased post procedural morbidity and mortality, some cases may be managed catheterbased using a covered stent[32-35].

Valve embolisation

Valve embolisation is reported in between 0.5-8% of TAVI procedures. [45] While embolisation into the left ventricle requires immediate surgical intervention, embolisation into the aorta can often be managed percutaneously with good results[45, 46] [V]. In cases where a second valve can be inserted in an acceptable position, there seems to be little if any clinical consequence, although long-term follow up is needed.[45]

Table 1:

Study	Valve Type	Access	Number of pts.	30 day mortality	Mean Log. EUROscore	Pacemaker frequency	Stroke <30 days
Piazza et al.[36]	CoreValve®	TF	646	8 %	23.1±13.8%	9.3 %	1.9 %
Khawaya et al.[15]	CoreValve®	TF	270	N/A	N/A	33.3 %	N/A
Zahn et al. [37]	CoreValve® & Edwards SAPIEN™	TA/TF	697	12.4 %	20.5±13.2 %	42.5 % CoreValve® 22 % SAPIEN™	2.8 %*
Olsen et al.[38]	CoreValve®	TF	20	5 %	21±16 %	25%	0 %*
Smith et al.[39] (PARTNER A)	Edwards SAPIEN™	TA/TF	348	3.4 %	29.3±16.5 %	3.8 %	4.7 %
Thomas et al.[40]	Edwards SAPIEN™	TA/TF	1038	8.5 %	27.6	7 %	2.5 %
Walther et al.[41]	Edwards SAPIEN™	TA	100	10 %	29.4±13 %	N/A	0 %*
Leon et al[42] (PARTNER B)	Edwards SAPIEN™	TF	179	5 %	26.4±17.2 %	3.4 %	6.7 %
Steigen et al.[43]	Edwards SAPIEN™	TA/TF	25	4%	27.1 %	N/A	0 %*
Johansson et al.[44]	Edwards SAPIEN™	TA/TF	40	5%	TA 23.5±17 %	N/A	7.5 %*
					TF 25.6±15		
Nielsen et al.[III]	Edwards SAPIEN™	TA/TF	100	8%	TA 21.5±13.5	4%	1 %
					TF 15.9±9.4		

*A summary of international and nordic transcatheter aortic valve implantation (TAVI) publications. TF: Transfemoral TAVI, TA: Transapical TAVI. *Procedural rate.*

Cerebrovascular events

Cerebral stroke is a major concern following TAVI. New ischemic brain lesions have been found on post procedural MRI scans in up to 70% of patients after femoral and apical TAVI, a risk that seems similar in both approaches.[47, 48] It appears that the risk of cerebrovascular incident is not only elevated during the procedure, but also within the first postoperative year despite dual anti-platelet therapy [V][39, 49]. In the PARTNER trial cohort A, patients randomised to TAVI had a significant higher risk of stroke or transient ischemic attack after 30 days than the SAVR patients[39]. This difference was unchanged after 1 year[39]. In cases where the event of stroke debuts after the immediate per- and postoperative period, it is unlikely to be embolisms from the perprocedural dilation of the native valve and may instead be stemming from newly formed embolisms at the THV or late re-release of calcified material from the native valve.

Strokes are often divided into major and minor strokes. Whereas minor strokes often have the potential for gradual recovery, major strokes on the other hand can be severely debilitating. The prognosis is most strongly correlated to the severity of the stroke and the patients age[50]. In this category of patients with advanced age and other comorbidities, stroke can be almost as devastating as mortality.

Cardiac interventions, including SAVR and PCI, also carry a risk of cerebral stroke. Whereas the risk of stroke following PCI is below 0.5%[51] the risk following SAVR is reported between 1-4%.[39, 52]

Coronary artery occlusion

Placing the THV in the right position is crucial, since the THV and native valve must fit within the aortic bulb and below the coronary ostia in order to secure unobstructed flow in the coronary arteries. In some cases, the placing of the THV has resulted in left main obstruction and acute ischemia, requiring surgical or catheter-based intervention [V][53]. While this complication also occurs during SAVR, it can more easily be avoided because of the direct visualisation of the coronary ostia during insertion of the valve.

Ways to improve future THVs

Current and next generation THVs are illustrated in Table 2.

Paravalvular and central leakage is a concern in catheter implantable valves. The addition of a cuff on the outer side of the stent-valve to reduce paravalvular leakage is being investigated in a few valve brands.[54-56]

The ability to reposition or even remove the THV during implantation is of great importance, as it may enhance the possibility for a more precise valve positioning, thereby increasing the safety of the procedure and performance of the valve.

Anchoring of the prosthesis is done by expansion against the aortic wall and the LVOT including the ventricular septum. The ventricular septum is a fragile region and inappropriate pressure may cause conduction disturbances. Implanting the valve in a higher position and improved THV designs are likely to reduce the risk of AV-block and pacemaker implantation.

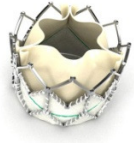
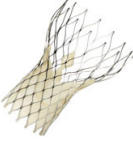

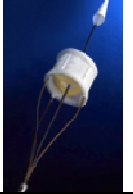

Intravascular umbrellas have been developed in order to protect mainly the carotid vessels from embolic material from the native valve[57].

International Results

Reports from catheter-based series have demonstrated promising results, with regard to quality of life improvements[58-60], procedural success rate and hemodynamic parameters [15, 36-38, 40-44, 61-63]. In Table 1 is listed an overview of currently published larger registries including the first 100 TAVI patients at our institution [III] and reports from other nordic centres [38, 43, 44]. The populations in these registries consist of elderly, fragile patients, with co-morbidities, with too high risk at conventional surgery. Short and longer-term follow-up have demonstrated sustainable hemodynamic improvement, and the few existing data on valve durability beyond 5 years have excluded significant valve deterioration. CT scans after 3 years post-implant, have excluded stent fracture, thrombus formation or visible leaflet calcification, fusion or thickening[64].

The value of TAVI is however not proven until longer-term durability has been assessed. The surgical bioprostheses are much

Table 2:

Valve	SAPIEN XT tm	Corevalve®	JenaValve tm	Direct Flow Medical®	Lotus tm Valve System
Design					
Status	>10.000 implants	>10.000 implants	Clinical investigation	Clinical investigation	Clinical investigation
Advantages	Low PM risk RCT data	Repositionable	Repositionable Retractable Anchors	Repositionable Retractable Cuffed Adaptable	Repositionable Retractable Cuffed

5 different valve models – including investigational devices. The list does not represent the authors’ recommendations; neither is the list a complete list of all available valves. The authors take no responsibility for the reported properties. RCT: Randomized controlled trial.

better documented, with rates of structural valve deterioration of only 25% at 15 years.[65-68]

The implanted valves have a high incidence of both paravalvular and central regurgitation. The regurgitation is most often mild to moderate, and appear to be unchanged over time.[22][IV] Our results, along with other reports, indicate that there are no significant clinical consequences of the degree of regurgitation within 12 months of follow-up [IV] [22, 69], however long-term consequences are uncertain. In treatment of patients unsuitable for surgical valve replacement this issue is of less importance, as TAVI results in a marked improvement of the prognosis compared to the alternative – standard medical treatment[42]. However, extending the TAVI technique to surgically operable patients necessitates a thorough analyses of the long-term consequences, since SAVR is a well-proven treatment option with an almost negligible degree of regurgitation.

Atrio-ventricular block requiring pace maker treatment is seen in 9-43% of CoreValve® implantations vs. 3,4-22% after SAPIENtm procedures[14, 15]. With the exception of need for permanent pacemaker treatment, the outcome after implantation of SAPIENtm and CoreValve® seems similar. AV block and need for pacemaker treatment is not a negligible complication. Pacemaker treatment is related to increased morbidity and risk of endocarditis[70, 71].

So far, there has been only one randomized trial evaluating TAVI treatment, the PARTNER trial consisting of 2 cohorts, A & B[39, 42]. In PARTNER cohort B, patients who were considered inoperable by conventional surgery due to high risk, were randomized to TAVI or standard medical treatment, including balloon dilatation. This study found reduced 1-year all-cause mortality in patients randomized to TAVI, with a hazard ratio of 0.55 in favour of TAVI, and a number needed to treat of 5[42].

In PARTNER cohort A, surgical high-risk patients were randomised to TAVI or SAVR. Randomisation was performed between F-TAVI and SAVR. Patients, where femoral access was not available, were randomised to A-TAVI and SAVR. The results from this cohort showed non-inferiority with regards to all-cause mortality after 12 months, p=0.001, but significantly increased risk of cerebral stroke or transient ischemic attack after 30 days and 1 year in the TAVI group (p=0.04)[39].

Level of evidence

A great number of reports from TAVI centres across the world have been published. The first articles were feasibility studies or case reports[7, 10, 12, 18, 72, 73] with low scientific evidence

level, but the majority of presently available TAVI publications are register-based (Table 1).

Even if results from registers are interpreted carefully, there will be a risk of bias stemming from the original referral of the patients and subsequent interpretation and registration of endpoints. This also applies to three of the attached papers in this thesis (I, III, IV).

The strongest and most reliable scientific evidence are obtained when clinical trials are performed under close monitoring, with randomisation to avoid selection bias, and endpoints are standardised and pre-specified for sustainable registration of outcomes. This applies to the clinical randomised controlled trial [V][39]. However, the implementation of multiple exclusion criteria may limit the generalisability of the study results and hence the external validity, and the conclusions from randomised trials must be carefully drawn.

In the PARTNER trial 8% of patients randomised to SAVR refused or withdrew from the study or declined surgical treatment compared to 0.3 % in the TAVI group[39]. This may lead to a selection bias, since the excluded patients potentially could have different demographics than the study population.

Review of papers underlying the thesis

The aim of this PhD-thesis has been to document the safety and quality of transcatheter aortic valve implantation, in order to establish its future role in the treatment of patients with aortic valve stenosis. This has been sought done through different categories of papers. The papers underlying the thesis are discussed in detail below, and the specific hypotheses for the five studies are as follows:

- 1: “Catheter-based aortic valve substitution. Initial experiences with stent valve implantation”:
It is possible to improve the clinical status and short-term survival of patients with aortic valve stenosis and too high risk at conventional cardiac surgery, by implanting a transcatheter heart valve in the aortic position through the left ventricular apex or via the femoral artery.
- 2: “Transatrial stent-valve implantation in a stenotic tricuspid valve bioprosthesis”:
It is technically feasible to implant a transcatheter heart valve inside a calcified, stenotic tricuspid valve bioprosthesis and improve the clinical status by relieving the stenosis.

3: "Single center experience with transcatheter aortic valve implantation using the Edwards SAPIEN™ Valve"

The hypotheses are that:

TAVI can be performed in patients with a surgical risk assessment that deems them unsuitable for SAVR

There is a demonstrable learning curve

Aortic valve area will be increased and valve gradient reduced
P-creatinine and cardiac biomarkers are temporarily increased after the procedure

4: "Aortic Regurgitation After Transcatheter Aortic Valve Implantation of the Edwards SAPIEN™ Valve"

TAVI carries a high risk of prosthetic valve regurgitation. The regurgitation is most often mild and has negligible clinical consequence.

5: "Nordic Study of Transapical Transcatheter Aortic Valve Implantation vs. Conventional Surgery – a Prospective Randomized Controlled Trial"

TAVI is superior to SAVR when treating patients aged over 75 years with isolated aortic valve stenosis with regards to mortality and morbidity

1: Catheter-based aortic valve substitution. Initial experience with stentvalve implantation.

Nielsen HHM, Andersen HR, Hjortdal VE, Klaaborg KE, Jakobsen CJ, Egeblad H, Terp K, Lindskov C, Sloth E, Poulsen SH, Boing I, Thuesen L. *Ugeskr Laeger* 2009;171:2277-2281

Background:

At the time of publishing this study, TAVI was in the first years after clinical introduction, and Skejby Hospital was the first Scandinavian centre to perform TAVI procedures. The study represents a feasibility study, performed on the basis of register data from the first 26 TAVI patients at our institution. The paper describes the F-TAVI and A-TAVI procedure techniques in detail, in order to inform clinicians from referring centres about the new treatment option for high-risk patients.

Hypothesis:

It is feasible to improve the clinical status and short-term survival of patients with aortic valve stenosis, by implanting a transcatheter heart valve in the aortic position through the left ventricular apex or via the femoral artery.

Material and Methods:

Data on age, sex, EUROscore and echocardiography parameters were drawn from patient files and a clinical database. Patients were categorised according to their preoperative NYHA class and compared to their corresponding 30-days condition. Echocardiography examinations were reviewed and analysed for valve performance.

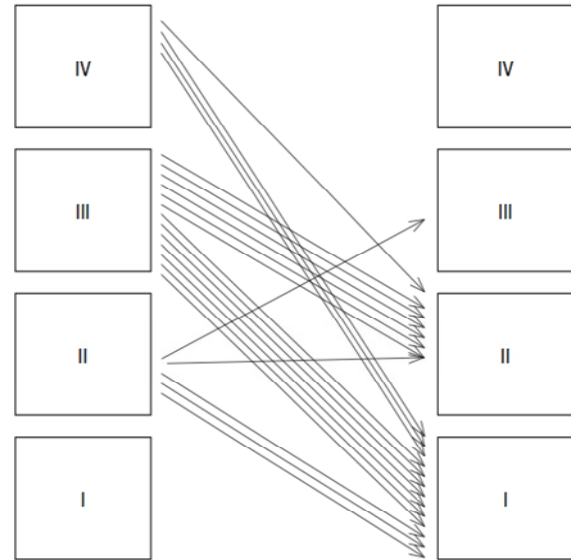
Results:

The procedural success rate was 75% in the F-TAVI group and 93% in the A-TAVI group. 30 days mortality rate was 25% and 7% in the F-TAVI and A-TAVI group respectively. 91% of patients improved their NYHA functional class (Figure 3). Both groups experienced an increase in the mean (±SD) aortic valve area from 0.6±0.13 cm² to 1.6±0.39 cm² in the F-TAVI group and from 0.7±0.2 cm² to 1.6±0.37 cm² in the A-TAVI group.

Limitations:

The study was register based and hence prone to selection bias. The sample size of only 26 patients limits the statistical validity of the results. Furthermore, the results are from the early introduction of the technique, performed by an inexperienced team.

Figure 3:



New York Heart Association function class before (left) and 30 days after the procedure (right).

Discussion:

Because the study was based on the early experience and a relatively small patient cohort, the results does not necessarily reflect the true quality and potential of the technique. After publishing this paper, the procedure technique has undergone several changes and fine-tuning at our centre. The team of cardiologists, cardiac surgeons, anaesthesiologists and vascular surgeons, are now more experienced and reduced in size. Vascular surgeons no longer participate, and cardiac surgeons are only present during A-TAVI. The aim of this study was however not to present the final edition of the procedure, as that was not possible at the time.

The paper was intended as a presentation of the new catheter based technique and attended clinicians working with patients with aortic valve stenosis. This was done in order to promote awareness of the new treatment option and increase referral of conventional inoperable patients. As such, the aim of the study was fulfilled.

Given the limited time frame for gathering of follow-data, long-term data could not be included in the study. However, the study could have been improved by extending the clinical descriptions of the patients. The inclusion of 6 minute walk tests before and after the procedure, risk scoring using STS score and more detailed valve performance descriptions with regurgitation grading after the procedure, were all parameters that would have improved the information level of the paper. Later data from other centres have shown that TAVI results in an improvement of 6 minute walk distance already after 30 days.[74]

Finally, more thorough statistical description of the data including between groups comparisons and testing would have been appropriate.

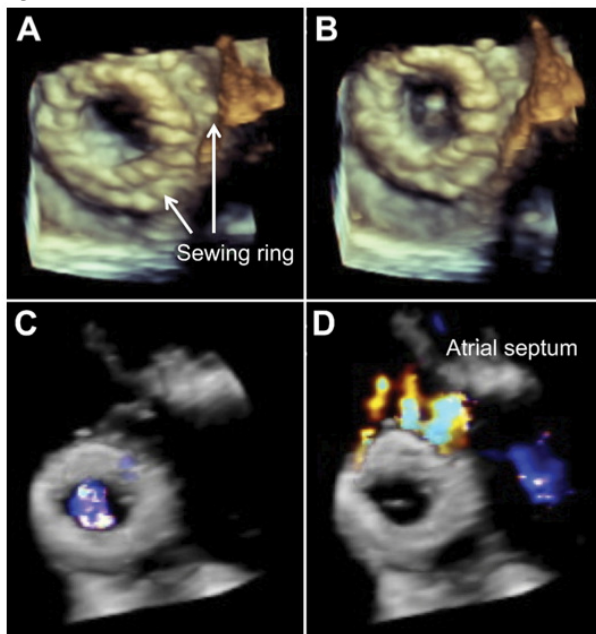
Since the publication of the paper, a vast amount of papers have confirmed our findings and the feasibility of the technique.[37, 39-44, 49, 63, 64]

Conclusion:

We found that it was possible to improve the clinical status and short-term survival of patients with aortic valve stenosis by implanting a transcatheter heart valve.

The study would have benefitted from a more thorough description of clinical and echocardiographic characteristics, however the purpose of the study, as a promotion of a feasible new treatment option for high-risk patients with aortic valve stenosis, was fulfilled.

Figure 4:



Three-dimensional transesophageal echocardiography 1 week after the valve-in-valve procedure. The stent-valve is seen from the atrial aspect, open and closed in (A) and (B), respectively. The unfolded nitinol framework of the stent-valve is seen within the sewing ring of the degenerated tissue valve. (C) Color Doppler shows the antegrade diastolic flow, and (D) three paravalvular jets appear in the systole close to the atrial septum.

2: Transatrial stent-valve implantation in a stenotic tricuspid valve bioprosthesis

Nielsen HHM, Egeblad H, Klaaborg KE, Hjortdal VE, Thuesen L. Transatrial stentvalve implantation in a stenotic tricuspid valve bioprosthesis. *Ann Thorac Surg* 2011;91:e74-76.

Background:

Transcatheter valve implantation was initially performed in the aortic valve position[8, 9]. The implantations have since then most often been performed to alleviate stenosis of native valves in either the aortic or the pulmonary position. The Valve-in-Valve technique was introduced as an alternative to conventional re-operation, in patients with a failed heart valve bioprosthesis[19, 20]. This paper was a case report, demonstrating the feasibility of the implantation of a THV inside a failed tricuspid valve bioprosthesis via a trans-atrial approach.

Hypothesis:

It is technically feasible to implant a transcatheter heart valve inside a failed calcified tricuspid valve bioprosthesis, to improve the clinical status by relieving the stenosis

Materials and Methods:

The patient file and echocardiographic examinations from the first patient undergoing tricuspid valve-in-valve implantation at

our centre were reviewed. Perioperative hemodynamic data and fluoroscopic images were analysed.

Results:

The patient underwent the procedure successfully, and was discharged in wellbeing. The implanted 26 mm THV resulted in an increase of the measured tricuspid valve area from 0.4 cm² to 2.5 cm². This caused a reduction in CVP from 34 mmHg to 18 mmHg and despite paravalvular regurgitation (Figure 4), markedly improvement of the clinical condition, with vanishing of ascites, peripheral oedemas and reduced need for diuretics.

Limitations:

The paper was a case-report with only one patient. The follow-up period was limited to the immediate in-hospital postoperative period.

Discussion:

Previous papers on valve-in-valve procedures have been published[21, 75-77]. The difference from the previously presented valve-in-valve publications relates to the different anatomical position. In this case a new approach had to be developed in order to introduce the valve in the tricuspid position. The case report is a way to present new therapeutical advances at an early stage. The often limited experience with the procedures and small sample sizes reduces the scientific level of evidence. However, it is a category of papers that hints the direction of future treatments, allowing for discussion and launching of more scientific evaluation of the techniques.

The present paper suffers from a short follow-up period and only one patient in the cohort. Increasing the follow-up period and sample size would strengthen the evidence level, and result in the presentation of a more final version of the procedure technique.

Conclusion:

While suffering from the inherent limitations of case-reports, the paper succeeds in presenting a new treatment modality for patients with failed bioprostheses in the tricuspid position.

3: Single centre experience with transcatheter aortic valve implantation using the Edwards SAPIEN™ valve

Nielsen HHM, Thuesen L, Egeblad H, Poulsen SH, Klaaborg KE, Jakobsen CJ, Andersen HR, Hjortdal VE. Single center experience with transcatheter aortic valve implantation using the Edwards SAPIEN Valve. *Scand Cardiovasc J* 2011.

Background:

The paper was based on the first 100 patients undergoing TAVI at our centre. At the time of writing the manuscript, no data from randomised clinical trials were available. The purpose of the article was to describe the expected postoperative course after TAVI, and to contribute to the pool of evidence from the increasing number of register based studies from centres worldwide.

Hypotheses:

TAVI can be performed in patients with a surgical risk assessment that deems them unsuitable for SAVR
There is a demonstrable learning curve
Aortic valve area will be increased and valve gradient reduced
P-creatinine and cardiac biomarkers are temporarily increased after the procedure

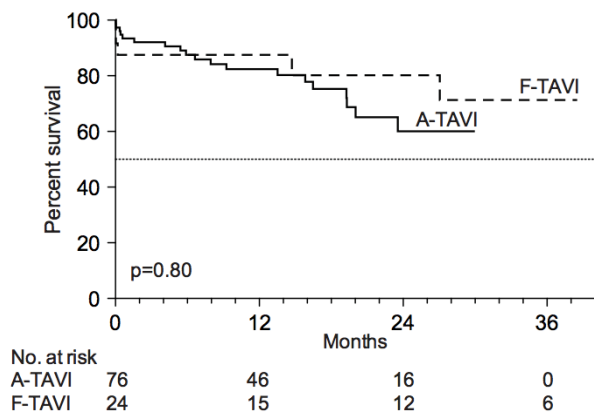
Materials and Methods:

The article was based on data from patient files, a clinical database and echocardiography examinations. Follow-up ranged from 30 days to 3 years, and mortality rates were complete for all patients. Blood samples were analysed for myocardial and renal biomarkers.

Results:

Overall procedural success rate was 92%. Thirty days mortality rate was 6.6% and 12.5% in the A-TAVI and F-TAVI group respectively. Survival after 1 year was 83% in the A-TAVI group and 88% in the F-TAVI group, although not statistically significantly different, $p=0.54$. (Figure 5)

Figure 5:



Kaplan Meier plot illustrating the cumulated survival following F-TAVI and A-TAVI.

Post procedural p-creatinine level increase and the release of cardiac biomarkers (TnT) was greater in the A-TAVI group than in the F-TAVI group, $p<0.001$ and $p<0.01$ respectively. Mean valve gradient decreased from 77 mmHg to 19 mmHg, and aortic valve area increased from 0.6 cm² to 1.6 cm². The mortality decreased from 12 % during the first 50 patients to 4% among the last 50 patients. Only one patient developed a stroke.

Limitations:

The study is register based with resulting selection bias. The patients were all considered too high-risk to undergo conventional surgery. The results improved over the study period, indicating a learning curve during the collection of data.

Discussion:

The study gives insight into the expected postoperative course and outcome, when performing either F-TAVI or A-TAVI on high-risk patients. The results correspond well with data from other publications[15, 36-38, 40-44, 61-63]. The stroke risk after SAVR procedures are reported between 0-5%[41, 78, 79]. However, all reported stroke rates in TAVI versus SAVR patients, are based on register-based studies. The only published series with randomised comparison between TAVI and SAVR found an increased risk of stroke or CVI in the TAVI group[39]. This increased risk was evident even at 12 months follow-up, raising concern on the potential thrombogenicity of the THVs, as the patients were in antithrombotic treatment at that time. Since a surgical valve can be implanted with a relatively low risk of stroke, TAVI will have to prove equally good in this aspect to be a realistic alternative. The results are gathered over a period of time affected by a learning curve. One could argue in favour of dividing the results into a

Table 3:

	Preoperative	Postoperative	p-value
Aortic valve area (cm ²)	0.6 (0.2)	1.6 (0.4)	<0.001
Peak gradient (mmHg)	77 (27)	19 (8.8)	<0.001

Hemodynamics before and after the procedure. Mean (SD)

Table 4:

Central leakage	43 %
Paravalvular leakage	60 %
Any leakage	79 %

Transcatheter heart valve performance post procedure. Mean (SD)

initial cohort, i.e. the first 50 patients, and a latter cohort. The results from the latter cohort would presumably be more reliable and representative, when interpreting the results for use in daily clinical decision-making. Furthermore, as the cohort consisted of high-risk patients, the results cannot be transferred to patients with lower risk profiles.

The release of cardiac enzymes after TAVI was significantly lower in the F-TAVI patients compared to the A-TAVI patients. Postoperative elevation of cardiac enzymes is also a well-known consequence after SAVR, where cardio-protective efforts have been implemented, in terms of repeated cardioplegia, shorter cross-clamp times etc[80, 81].

The increase in p-creatinine levels following TAVI was greater among A-TAVI patients than F-TAVI patients. Acute renal failure is a well-known risk after SAVR as well, and has been attributed to insufficient renal perfusion during cardiopulmonary bypass along with an immunological response [82]. Since cardiopulmonary bypass is avoided during TAVI, this reduces the risk of postprocedural renal failure, although the use of x-ray contrast counteracts this advantage.

Conclusion:

The paper documents that TAVI is feasible in patients with too high surgical risk and results in clinical and hemodynamic improvements. The procedure results in a release of cardiac enzymes and increased p-creatinine level. There is a learning curve when implementing the technique.

4: Aortic Regurgitation After Transcatheter Aortic Valve Implantation of the Edwards SAPIEN™ Valve

Nielsen HHM, Egeblad H, Andersen HR, Thuesen L, Poulsen SH, Jakobsen CJ, Klaborg KE, Hjortdal VE [in preparation].

Background:

The majority of papers on TAVI have procedural success rates, short-term mortality rates and clinical improvements as their main focus. Though many of the papers report echocardiographic evaluation of the valve performance, few reports exist with detailed description of the risk and consequence of paravalvular regurgitation after TAVI[22, 69]. The available studies are all register based and show that regurgitation after TAVI in most cases are constant. In one study, severe regurgitation was a predictor of increased risk of in-hospital death, respiratory and low cardiac output[69].

We have previously found that regurgitation after TAVI was present in 79 % of patients [III]. The clinical consequence is however unknown. Risk factors for regurgitation after THV implantation is also poorly investigated.

The aim of this study was to examine whether pre-operative predictors of increased risk of prosthetic regurgitation after THV Implantation were identifiable, and to determine any clinical consequence of regurgitation within the first postoperative year.

Hypothesis:

TAVI carries a high risk of prosthetic valve regurgitation. The regurgitation is most often mild and has negligible clinical consequence.

Material and methods:

Echocardiographic examinations of 100 consecutive patients were analysed. On pre-implant images, the THV landing zone in the left ventricular outflow tract was screened for potential preoperative risk factors for regurgitation, i.e. calcification of the anterior mitral leaflet, subvalvular muscular hypertrophy and asymmetrical calcification of the native valve.

Paravalvular and central regurgitation area were measured on post-implant images and summarised. Patients were divided into regurgitation severity on basis of their total regurgitation area, and compared to left ventricular measurements and the clinical course.

Results:

In our study, 75% of all patients had prosthetic valve regurgitation. The severity of the regurgitation appeared unchanged over the one-year follow-up period and did not correlate with postoperative need of diuretics. Moderate to severe regurgitation was associated with significant dilatation of the left ventricle and lesser NYHA class improvement than patients with none to mild regurgitation.

Asymmetrical native valve calcification increased the risk of paravalvular regurgitation non-significantly.

Limitations:

The echocardiographic examinations were retrospectively reviewed. The grading of regurgitation severity was based on regurgitation area only. Follow-up was limited to 1 year. The number of patients in the cohort was only 100 patients.

Discussion:

Even though a great number of patients experienced regurgitation after TAVI, it seemed to have little, if any, impact on their clinical status. However, as follow-up was limited to only 1 year, no predictions of the long-term effects of regurgitation can be made.

Among patients with none or mild regurgitation, 80% improved their NYHA class after the procedure, compared to 60% in patients with moderate or severe regurgitation ($p < 0.05$ one-tailed). It is possible, that the observed small differences in NYHA class and left ventricular measurements between patients with low versus high levels of regurgitation, will have a negative effect over a longer observation period.

The classification of prosthetic regurgitation is difficult and controversial. Many suggestions for criteria have been made[83, 84], but even newly released guidelines lacks quantitative criteria[85]. The classification made in this study uses only one criterion, namely total regurgitation area. Even if this approach is simple, it is highly quantitative. Furthermore the findings in our cohort of increased left ventricular volume and less clinical improvements in patients with severe regurgitation, supports the classification.

Conclusion:

The paper documents the substantial risk of prosthetic regurgitation after TAVI. While most patients have some degree of prosthetic regurgitation and the regurgitation was correlated with dilatation of the left ventricle, there seems to be little if any clinical consequence hereof.

5: Nordic Study of Transapical Transcatheter Aortic Valve Implantation vs. Conventional Surgery – a Prospective Randomized Controlled Trial

Nielsen HHM, Thuesen L, Hjortdal VE. [in preparation]

Background:

The majority of published scientific papers on TAVI have been register-based studies. Only 1 randomised controlled trial with 2 randomisation arms on TAVI have been published, the PARTNER trial[39, 42]. Due to the trial design of PARTNER and the visitation pattern in TAVI, patients with small femoral artery diameter and hence possible arteriosclerotic disease are referred for A-TAVI, whereas patients with sufficient femoral artery diameter are treated with F-TAVI. There is a need for an unbiased validation of the apical transcatheter implantation technique. The purpose of this study was to compare transapical TAVI to SAVR in a randomised clinical trial.

Hypothesis:

TAVI is superior to SAVR when treating patients aged over 75 years with isolated aortic valve stenosis.

Material and methods:

The study was a prospective randomised controlled trial with 1:1 randomisation ratio between A-TAVI and SAVR. The study was designed as a superiority trial in favour of A-TAVI. The primary endpoint was a combined endpoint consisting of all cause mortality, CVI and renal failure requiring dialysis within 30 days post procedure. Secondary endpoints included length of stay, echocardiographic evaluation of the valve prosthesis and left ventricular function, along with quality of life assessments.

We expected an endpoint rate of 13.5% in the SAVR group and 2.5% in the A-TAVI group, requiring a sample size of 96 patients in each group to document a difference with $p < 0.05$. Patients over 75 years of age and isolated aortic valve stenosis were included. Exclusion criteria included prior heart surgery, need for revascularisation and renal failure requiring dialysis.

Results:

The study was stopped prematurely after the inclusion of 59 patients at the study-initiating centre due to a non-significant trend towards more major adverse events in the A-TAVI group. The primary endpoint rate was 14.3% in the A-TAVI group versus 3.3% in the SAVR group, $p = 0.14$. Thirty days mortality rate was 3.6% and 0% in the A-TAVI and SAVR group respectively, $p = 0.3$. The incidence of cerebral stroke within 30 days was 7.1% in the A-TAVI group versus 3.3% in the SAVR group, $p = 0.5$. Two patients in the A-TAVI group were converted to SAVR due to severe prosthetic regurgitation. One patient required immediate conversion and homograft insertion due to aortic annular rupture. One A-TAVI patient received two valves, as the first valve embolised into the ascending aorta.

Limitations:

The cohort only included 59 patients, as the study was closed prematurely. The event rates used for power- and sample size calculations were based on previous results in very high-risk

patients not comparable to the study population. In contrary to the existing experience at the time of planning the study [1], completely new and unanticipated important events occurred during the study period, and conversions from TAVI to SAVR due to regurgitation and aortic annular rupture emerged.

Discussion:

At the time of commencing the study, TAVI was still a nascent technique. An increasing number of papers on TAVI were published, but all were based on high-risk patients [12, 18, 36, 61, 86-88] and no randomised clinical data were available. Consequently, no information without selection biases on lower risk patients was published. This study was designed to address both of these issues.

The study was launched simultaneously with a parallel study in east-Denmark, randomizing patients between SAVR and F-TAVI using the Corevalve® prosthesis. The two studies recorded identical clinical parameters and was planned to provide a combined evaluation of the two TAVI approaches compared to SAVR. To increase the internal validity of the study, patients with need for revascularisation were excluded. Additionally, so were patients with renal failure and need for dialysis. While increasing the homogeneity of the cohort, the in- and exclusion criteria made the estimation of expected endpoint rates much more difficult. Not only did the endpoint rate in the TAVI group considerably exceed the expected, but the results from the SAVR cohort were better than expected, with no re-operations, no mortalities within 30 days, and no incidence of renal failure with need for dialysis. In cohort A of the PARTNER trial, the SAVR group exhibited greater rates of death, stroke and renal failure than in our cohort[39][V]. As such, the results from the SAVR group in this study may represent extraordinary outcomes as a cause of chance.

Ending a study prematurely, leads to many ethical considerations. One can argue that the patients, who experienced complications, did so in vain, as results with no clinical significance are useless. However, the ethical problems are greater when continuing a study, in which there is a clear trend towards worse outcome in the intervention group.

The reason for the surprisingly disappointing outcome in this group of patients with lower surgical risk is still not clear. If not attributable to statistical uncertainties, it could be hypothesised, that patients with a lower risk profile and age, have a different aortic pathology, with higher risk of annular dissection or rupture. One could speculate that higher-risk patients - than the ones included in this study - might be better suited for TAVI, as their aortic annulus might be more calcified, resulting both in improved fixation after dilatation of the valve and easier identification of the correct level of implantation. This could mean that the patients included in this study may not necessarily be the most suitable subjects for TAVI and should in any case be treated by the most experienced team.

Another explanation could be that TAVI, in its present form, have a finite risk regardless of the patients risk profile, caused by the technical shortcomings of the available devices, with regards to positioning, retraction and regurgitation risk.

On a balanced view we found it was correct to stop the study and re-think the design of the investigation.

The power of a future study should be a non-inferiority study based on contemporary results. Not only for TAVI - but also SAVR procedures, and in patients matching the population included in the investigation. Furthermore, a new study should be based on the newest and hopefully improved valve designs, capable of solving the shortcomings of the present generation of TAVI de-

VICES. With better valve designs, more available sizes and better preoperative measurements of the aortic annulus using CT, the risk of paravalvular regurgitation is expected to decrease. With decreasing event rate in the TAVI group, the sample size would increase, in order to document non-inferiority, which would require a large volume of procedures in several centres. If non-inferiority between SAVR and TAVI could be proven with regards to both postoperative mortality and morbidity, one should weigh the increased expenses presently associated with TAVI towards the modest benefit of increased short-term quality of life, that for now seem to be the only improvement over SAVR.

Conclusion:

The study was stopped prematurely, without reaching statistical significant differences in the primary endpoint rates. Hence, it failed to complete the aim of proving TAVI to be superior to SAVR. Despite the non-significant differences between the groups, the trend towards more adverse events in the TAVI group is worrying and must lead to further investigations, before extending the indications for TAVI to lower risk patients.

Whom to treat?

Patients should be treated according to present guidelines, based on existing scientific evidence. Surgical aortic valve substitution has been performed for more than 30 years and is the first choice when treating significant aortic valve stenosis. The procedure is effective and safe, with mortality rates ranging from 2.5 % to 15 %, depending on the risk profile of the population[39, 52, 89, 90]. Early TAVI publications, including the PARTNER trial cohort B[42], established that TAVI is superior to medical treatment in patients who cannot undergo SAVR because of high risk. These results cannot be transferred to lower risk patients, who have the option of undergoing SAVR[91-94].

The A cohort from the PARTNER study and the STACCATO trial included operable low to high-risk patients. Short-term results (<12 months) indicate that TAVI seems to be a relevant alternative to SAVR in high-risk patients, when looking at procedural success- and mortality rates alone. Despite this, TAVI procedures may not match SAVR in high-risk patients when considering the overall morbidity risk. The higher risk of cerebral events and valve regurgitation is not competitive with SAVR. Even if regurgitation in mild to moderate cases may not have a clinical effect on the short term [IV], there is currently no data on the potential long-term consequences of regurgitation, this being in a 70-year old patient, who may live another 10 years or more.

However, TAVI results are expected to improve with increasing experience and optimized devices[62].

New studies have investigated potential outcome predictors in TAVI populations[42, 95]. Patients with peripheral vascular disease, oxygen dependent COPD or left ventricular function over 55 % may not benefit substantially from TAVI compared to standard medical treatment[42].

Independent risk factors for worse outcome following TAVI includes LVEF <50%[24] and impaired renal function[96].

Perspectives

Modern medicine strives to make treatments safer, more effective and less invasive and TAVI is an example of this tendency. The devices are still in their early generations, but the industry is investing vast efforts into developing new and better valves and catheters.

The described technical shortcomings of the TAVI devices are all potentially solvable. As devices become more controllable, with precise positioning and possible retrieval and repositioning and when improved valve designs have minimized the risk of prosthetic regurgitation and conduction disturbances, TAVI may well become a sensible choice of treatment in patients with aortic valve stenosis – and potentially also regardless of age and risk profile.

Conclusion

Transcatheter aortic valve implantation has proven feasible, and there is scientific evidence, supporting that TAVI should be offered to patients with aortic valve stenosis, who are not candidates for SAVR due to high predicted operative risk.

The role of TAVI in lower risk patients remains controversial, as surgical aortic valve replacement offers safe and effective relief from aortic valve stenosis while TAVI still suffer from a few device related technical shortcomings and increased risk of cerebral events. The definition of the border between SAVR and TAVI is an ongoing and moving target of investigation.

SUMMARY

Transcatheter aortic valve implantation (TAVI) was introduced experimentally in 1989, based on a newly developed heart valve prosthesis – the stentvalve. The valve was invented by a Danish cardiologist named Henning Rud Andersen.

The new valve was revolutionary. It was foldable and could be inserted via a catheter through an artery in the groin, without the need for heart lung machine. This allowed for a new valve implantation technique, much less invasive than conventional surgical aortic valve replacement (SAVR).

Surgical aortic valve replacement is safe and improves symptoms along with survival. However, up to 1/3 of patients with aortic valve stenosis cannot complete the procedure due to frailty. The catheter technique was hoped to provide a new treatment option for these patients.

The first human case was in 2002, but more widespread clinical use did not begin until 2006-2010. Today, in 2011, more than 40.000 valves have been implanted worldwide. Initially, because of the experimental character of the procedure, TAVI was reserved for patients who could not undergo SAVR due to high risk. The results in this group of patients were promising. The procedural safety was acceptable, and the patients experienced significant improvements in their symptoms. Three of the papers in this PhD-thesis are based on the outcome of TAVI at Skejby Hospital, in this high-risk population [I, II and IV]. Along with other international publications, they support TAVI as being superior to standard medical treatment, despite a high risk of prosthetic regurgitation.

These results only apply to high-risk patients, who cannot undergo SAVR.

The main purpose of this PhD study has been to investigate the quality of TAVI compared to SAVR, in order to define the indications for this new procedure. The article attached [V] describes a prospective clinical randomised controlled trial, between TAVI to SAVR in surgically amenable patients over 75 years of age with isolated aortic valve stenosis.

The study was terminated prematurely, as patients undergoing TAVI showed a statistically non-significant trend towards more

complications than SAVR patients. Although non-significant the study was closed for ethical reasons.

At present, scientific evidence supports TAVI as being superior to standard medical treatment, in patients who cannot undergo SAVR due to high- predicted risk. However, in patients who are surgically amenable, current publications suggest that TAVI using presently available devices is not competitive to SAVR, with regards to procedural safety and outcome.

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