One-year interim follow-up results of the TRAVERCE trial: the initial feasibility study for trans-apical aortic-valve implantation

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Abstract

Objectives: To evaluate the interim results of the initial multicenter feasibility trial for trans-apical aortic-valve implantation (TA-AVI) in high-risk elderly patients with severe aortic stenosis. Methods: A total of 168 patients were prospectively included in three European centers between February 2006 and April 2008. The Cribier–Edwards or Edwards SAPIEN Trans-catheter Heart Valve (23 mm and 26 mm) was implanted using an oversizing concept. Interventions were performed in a hybrid operative room (OR) (one center), with a mobile C-arm in the OR (one) and in the catheterization laboratory (one). Inclusion criteria included age >70 years and an increased risk profile (additive European System for Cardiac Operative Risk Evaluation (EuroSCORE) >9). Results: Patient age was 82.1 ± 5.6 years, 76% were female and the EuroSCORE was 11.3 ± 1.8 (additive) and 27 ± 12.7% (logistic). Cardiopulmonary bypass was used by intention in 14.2% during the initial phase, secondarily in 10.1% and 75% of the patients were treated off-pump. Valve implantation led to a good immediate result in 161 (95.8%) patients and problems were encountered in seven patients (malposition (two patients), migration (three patients) and severe incompetence (two patients)). Nine patients were converted to conventional surgery, early stroke occurred in two (1.2%) patients and 10 (6%) patients received a new pacemaker. At 30 days, 25 patients died, 1010-7940/$ — see front matter © 2010 European Association for Cardio-Thoracic Surgery. Published by Elsevier B.V. All rights reserved.

Keywords: Aortic valve; Valve replacement; Trans-catheter; Trans-apical; Minimally invasive

1. Introduction

Conventional aortic-valve replacement is indicated in most patients with symptomatic aortic stenosis (AS) and is currently being performed with acceptably low risk and good long-term outcomes [1,2]. Elderly patients with additional co-morbidities, however, may have an increased risk profile for a conventional approach including sternotomy, cardiopulmonary bypass and temporary cardioplegic cardiac arrest [3,4]. To offer a potentially better therapeutic option, new minimally invasive trans-catheter techniques that allow for off-pump beating heart aortic-valve implantation (AVI) have been developed [5–8]. By means of a retrograde transfemoral (TF) or an antegrade trans-apical (TA) approach, the native aortic leaflets can be balloon-dilated and a stent-based xenograft implanted. Meanwhile, both the CoreValve™ prosthesis (CoreValve Inc., Irvine, CA, USA) and the Edwards SAPIEN™ prosthesis (Edwards Lifesciences LLC, Irvine, CA, USA) have obtained European commercial approval. Current recommendations from European medical societies (European Society of Cardiology and European Association for Cardiothoracic Surgery) concur that there is an indication to perform trans-catheter AVI in elderly patients with an increased risk profile [9]. While acknowledging that the logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) may be overestimating, the individual patient’s risk and patients with a 15% or higher risk profile are common candidates for trans-catheter AVI.

Herewith, we present the interim acute and 1-year follow-up results of the first feasibility trial for TA-AVI performed at three centers initiated and enrolled in the pre-commercial...
era between 2006 and 2008. This study will follow surviving patients for 5 years and is sponsored by Edwards Lifesciences LLC, Irvine, CA, USA.

2. Methods

2.1. Pre-trial preparation

Prior to starting this clinical feasibility trial, experimental in vitro and in vivo animal testing on the potential feasibility of using a TA approach for the implantation of a stent-based balloon-expandable trans-catheter xenograft was performed in Irvine, CA and in Leipzig, Germany [10,11]. Before starting the clinical study, the investigators agreed that older age (≥70 years) and presence of comorbidities, producing an additive EuroSCORE of 9 or higher would justify the use of this new technique. This concept, for patient inclusion, was presented and approved by the local ethical committees. All patients gave written informed consent after receiving verbal and written study details, which included the fact that this was a new procedure. All patients consented for potential conversion to conventional sternotomy as well as possible ‘bail-out’ surgery.

2.2. Site prerequisites

Prior to study initiation, a dedicated trans-catheter team, consisting of cardiac surgeons, cardiologists and cardiac anaesthetists, was established at each site. The procedures were performed in a hybrid operative theatre, in a catheterization laboratory with sterile conditions and in the regular operative theatre with C-arm imaging at one center each. These facilities enabled quick heart—lung-machine access and conventional operation, if required. Trans-oesophageal echocardiography (TEE) was available at every site. Frequent communication between the sites allowed for sharing specific learnings throughout the study, which was especially helpful during the initial period to develop specific ‘bail-out’ solutions for potential procedure-related complications. After some experience, the procedures were performed in a standard manner as described previously [12].

2.3. Study device

The Cribier–Edwards trans-catheter xenograft manufactured with equine pericardium was used in the initial patients together with the 33-F TA delivery system (Ascendra™, both Edwards Lifesciences, Irvine, CA, USA). From mid-2007 onwards, a 26-F TA delivery sheath and the Edwards SAPIEN™ THV xenograft with ThermoFix™-processed bovine pericardium were used. All patients included in this study were treated under an oversizing protocol, which implied that a valve at least 2 mm larger than the native annulus was implanted. According to this protocol, a patient with an aortic-annulus diameter ≤21 mm was scheduled to receive a 23-mm prosthesis and a patient with an aortic-annulus diameter from 22 to 24 mm was scheduled to receive a 26-mm prosthesis.

2.4. Initial experience

Four patients (not included in the 168-patient study) were enrolled and treated under a first version of the ethics-committee approved clinical protocol in 2004 and 2005 without using an oversizing implantation procedure. Three of these four patients were converted the same day; two, during the index procedure and one, some hours later, all due to significant paravalvular leakage and resulting in aortic insufficiency. In the fourth patient, mitral-valve injury occurred due to apical wire chordae entanglement before positioning the valve, thus necessitating conversion to conventional double-valve surgery. Due to these failures, enrollment was stopped in summer 2005, and experimental testing was repeated with iterated products including a 26-mm valve and the establishment of an oversizing protocol. The amended study protocol, upon which this study is based, was submitted and approved by the local ethical committees at the end of 2005.

2.5. Patient population

A total of 168 high-risk patients were included at three sites from February 2006 until April 2008. Main inclusion criteria were older age (≥70 years) and the presence of an increased risk profile, as defined by an additive EuroSCORE ≥9. In addition, presence of porcelain aorta was an inclusion criterion. Patient demographics, as well as risk profiles, are shown in Table 1. In addition, specific cardiac and vascular risk factors are provided in Table 2. All patients gave written informed consent for participation in the study after receiving verbal and written information on all study details, including specifics related to participation in a feasibility trial for initial human application.

2.6. Data management and statistical analysis

All study data were documented prospectively on case-report forms and entered in a specific database, following monitoring by the sponsor. Adjudication of deaths and adverse events are conducted by an independent Clinical Events Committee. Data are presented as means ± standard deviation and as percentages, wherever appropriate. The probabilities of outcome variables were calculated using the Kaplan–Meier method. A p < 0.05 was considered to indicate statistical significance. The results presented are an interim analysis as of 24 August 2009.

Table 1. Patient demographics (n = 168).

<table>
<thead>
<tr>
<th>Age [years]</th>
<th>82.1 ± 5.6 [63—95]</th>
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<tbody>
<tr>
<td>Female</td>
<td>127 (76%)</td>
</tr>
<tr>
<td>NYHA III</td>
<td>121 (72%)</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>42 (25%)</td>
</tr>
<tr>
<td>Body weight [kg]</td>
<td>64.7 ± 13.1</td>
</tr>
<tr>
<td>Height [cm]</td>
<td>161.7 ± 8.1</td>
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<tr>
<td>Additive EuroSCORE</td>
<td>11.3 ± 1.8 [range 7—17]</td>
</tr>
<tr>
<td>Logistic EuroSCORE</td>
<td>27 ± 12.7 [range 7—72]</td>
</tr>
<tr>
<td>Aortic-valve area [cm²]</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>Mean gradient [mm Hg]</td>
<td>43 ± 17</td>
</tr>
<tr>
<td>Ejection fraction [%]</td>
<td>53 ± 16 [range 15—82]</td>
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</tbody>
</table>
3. Results

All implantations were performed by a team of cardiac surgeons, cardiologists and cardiac anesthetists, together with operative-theatre nurses, anesthesia nurses, catheterization laboratory technicians and cardiac perfusionists. The heart—lung machine was readily available in all cases. In the beginning phase of the trial, the procedure was intentionally performed with on-pump femoro—femoral cannulation in a total of 24 (14.2%) patients. Thereafter, only femoral access wires were placed, allowing the immediate conversion to cardiopulmonary bypass during the procedure, which could be accomplished in 11 (7.6%) patients, five of whom died at 30 days (45%). Reasons to initiate cardiopulmonary bypass were haemodynamic instability, coronary impingement and occlusion, suboptimal initial valve position and valve dysfunction. A total of 133 (79%) patients were treated in a completely off-pump manner.

TA access was feasible in all patients. A total of 46 (27.4%) patients received a 23-mm trans-catheter prosthesis and 122 (72.6%) patients a 26-mm prosthesis. The mean native aortic annulus diameter, as measured by TEE, was 22.4 ± 1.4 mm. Given a mean study-valve diameter of 25.2 ± 1.3 mm during the procedures, an oversizing of 2.7 ± 0.9 mm was performed.

TA-AVI was performed as intended in 161 (95.8%) patients. However, complications occurred that are listed in Table 3. Additional complications that were encountered include: cardiac failure requiring temporary intra-aortic balloon-pump support in three (1.8%) patients; extracorporeal membrane oxygenation (ECMO) support was later initiated in two of them. Myocardial infarction occurred in two (1.2%) patients, stroke in four (2.4%) patients and renal failure requiring temporary dialysis in 23 (13.4%) patients. Preoperatively, 15.5% of the patients had a permanent pacemaker. In addition, 10 (6%) patients required new onset pacemaker implantation in the early postoperative period.

At 30 days, a total of 25 (14.9%) patients had died, and at 1 year, an additional 33 patients were dead, whereas, after the most recent data analysis in August 2009, 65 deaths have been reported. The overall survival was 85% at 30 days and 63% at 1 year. The 1-year Kaplan—Meier survival curve is shown in Fig. 1.

Causes of death at 30 days were cardiac in 48% (cardiac failure in 10 patients, arrhythmia in one patient, sudden death in one patient), respiratory in 12% (three patients), neurological in 4% (one patient) and other in 36% (multi-organ failure in four patients, abdominal complication in three patients, sepsis in two patients). At 1 year, causes of death were cardiac in 39.4% (13 patients), respiratory in 18.2% (six patients), neurological 9.1% (three patients), unknown in 6% (two patients) and other in 27.3% (nine patients). An overview of the overall survival and the freedom from myocardial infarction, stroke, explantation or structural-valve degeneration is given in Table 4.

ECHOCARDIOGRAPHY revealed well-preserved ejection fraction as well as low transvalvular blood flow velocities and low gradients and sufficiently good aortic-valve orifice areas in all reporting implanted devices. Details are given in Table 5. Approximately 50% of the patients presented with some degree of aortic-valve incompetence, usually paravalvular and of minor severity. Details are given in Fig. 2. All patients improved regarding their functional status up to 1-year follow-up.
Table 4. Overview on results for the whole population of 168 patients.

<table>
<thead>
<tr>
<th>%</th>
<th>30 days</th>
<th>6 months</th>
<th>1 year</th>
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<tbody>
<tr>
<td>Overall survival</td>
<td>85</td>
<td>70</td>
<td>63</td>
</tr>
<tr>
<td>Freedom from myocardial infarction</td>
<td>99</td>
<td>97</td>
<td>96</td>
</tr>
<tr>
<td>Freedom from stroke</td>
<td>98</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>Freedom from explant</td>
<td>96</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>Freedom from structural-valve dysfunction</td>
<td>100</td>
<td>100</td>
<td>100</td>
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Table 5. Echocardiographic results.

<table>
<thead>
<tr>
<th></th>
<th>Pre-op</th>
<th>Post-op</th>
<th>3–6 months</th>
<th>1 year</th>
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<tbody>
<tr>
<td>EF [%]</td>
<td>53 ± 16</td>
<td>52 ± 15</td>
<td>56 ± 14</td>
<td>56 ± 14</td>
</tr>
<tr>
<td>$P_{\text{max}}$ [mm Hg]</td>
<td>70 ± 24</td>
<td>61 ± 7</td>
<td>17 ± 9</td>
<td>16 ± 8</td>
</tr>
<tr>
<td>$P_{\text{mean}}$ [mm Hg]</td>
<td>43 ± 17</td>
<td>8 ± 4</td>
<td>9 ± 5</td>
<td>9 ± 5</td>
</tr>
<tr>
<td>AOA [cm²]</td>
<td>0.6 ± 0.2</td>
<td>1.3 ± 0.5</td>
<td>1.3 ± 0.4</td>
<td>1.3 ± 0.4</td>
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</table>

4. Discussion

TA-AVI was introduced as a therapeutic option for high-risk patients with symptomatic aortic stenosis in late 2004, after initial experimental testing and animal implantations [10,11]. Patient indications identified at that time, including an additive EuroSCORE of 9 or higher, have proven to be realistic, even considering recent publications that EuroSCORE overestimates risk [13]. However, the initially defined parameters have led to the inclusion of high-risk patients only, which is in accordance with the current position statement [9].

Before starting this trial in 2006, the outcomes of the initial four patients treated without device oversizing were discouraging. As a result, the Ethics Committee recommended a temporary halt to the study to re-evaluate the procedure and perform additional testing. The device was subsequently iterated and learnings, including valve oversizing were applied, which allowed the successful continuation of the study in early 2006.

The initial goal of this study was to evaluate the feasibility of treating symptomatic aortic stenosis in high-risk elderly patients, using a minimally invasive approach. By means of a stepwise development of the TA-AVI procedure, a good standard of care has been obtained that allows the avoidance of a median sternotomy and the implantation of an aortic-valve xenograft, using a truly minimally invasive and off-pump technique [12]. Thus, the major goal of this study, to test the feasibility of trans-apical antegrade and direct off-pump AVI, has been achieved.

The overall results, however, should be evaluated with specific attention. There was a substantial overall mortality at 30 days and at 1 year. This can, in part, be explained by the infancy of the technology at the start of the study. First, this was the first clinical trial on TA-AVI. As a result, there was neither the knowledge of how to avoid complications that may be inherent to the specific procedure, nor the knowledge of how to appropriately screen and treat elderly and high-risk candidates. Some solutions to peri-procedural complications, for example, the use of a valve-in-a-valve implantation in case of leaflet dysfunction or in the case of very low initial positioning have been developed during the course of the study. Further aspects on optimal positioning and controlled implantation have been developed throughout the study, most of which have allowed us to delineate some standard of procedure for TA-AVI [12]. Knowledge of all of these specific aspects of the procedure, together with the use of some specific techniques, will lead to better results of TA-AVI for any center that has just begun its experience with this technology. In view of the lack of experience with TA-AVI at the commencement of this study, the acute results of the trial must be judged successfully. In parallel, although the 1-year outcomes may also be initially somewhat unsatisfying, we should keep in mind that very high-risk patients were treated. The additional mortality between 30 days and/or hospital discharge and 1-year follow-up is an obvious reflection of the overall multiple co-morbidities of the patients. Optimal screening, together with the use of improved scoring systems, will most likely lead to an even better understanding of which patients may benefit from trans-catheter AVI in the future.

In this study, we observed a relatively high rate of apical bleedings, which was due to some technical problems with the purse-string sutures. After some refinements, these issues could be solved, leading to very safe apical access in the second half of this trial. The imaging used was different between the three centers. Whereas sufficient visualization could be obtained with the use of a mobile C-arm at one center, it became clear throughout the study that high-quality imaging with catheterization laboratory standard, which can, at best, be obtained in a hybrid operative theatre, is the ideal prerequisite for performing trans-catheter AVIs. Use of a hybrid operative theatre should therefore be recommended. In case this is not feasible, trans-catheter AVI in a catheterization laboratory under sterile conditions can be an (temporary) alternative.

When discussing the strategy on how to perform trans-catheter AVI, in particular, on whether to use a TF or a TA approach, there is, at present, no substantial evidence to prefer a TF over a TA implantation approach in high-risk patients with aortic stenosis. Unfortunately, to date, no randomized trial has been conducted comparing TF and TA trans-catheter AVI with conventional surgery in a randomized ‘three-armed’ study design. Therefore, comparisons with other series, especially to series describing results of the TF approach alone cannot be made.
Acknowledgement

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References


Appendix A. Conference discussion

Dr. A. Wechsler (Philadelphia, Pa): I think we all appreciate that this was a pioneering and courageous study and as you showed, things have certainly gotten a lot better. So I have just a few very simple questions for you.

The first is, am I correct in assuming that you are reporting the results by intention-to-treat? You have included all the patients in the results?

Dr. Walther: Sure, all patients that were intended underwent the procedure. This is all intention-to-treat.

Dr. Wechsler: Can you tell us what happened to the nine patients who required open heart surgery?

Dr. Walther: Well, I didn’t do a subanalysis of them because I don’t have data from all the centers on what specifically happened to them. I looked at those we had to convert, and of those we had to convert where we had to go on-pump and then convert, we converted five cases in Leipzig, so far three of them survived and, of those, we had to convert to the pump for haemodynamic deterioration. This is not all who underwent a sternotomy later on. Forty-five percent died at 30 days and 55% made it to discharge at 30 days in good condition.

So the summary on that would be that if you have a problem during the procedure, either you need to go on-pump or need to convert to conventional surgery. Of course, your risk is higher, but 50% plus can be saved. So it is a clear indication to do these procedures in a hybrid room to be able to save the lives of those patients.

Dr. Wechsler: And you reported your results as 30-day mortality, which means different things to different people. Was that the same as hospital mortality?

Dr. Walther: With the exception of two patients, yes. There was one patient who stayed very long, until day 120, in our center, was discharged, came back and forth, and then died due to I don’t remember. But it is in-hospital or 30-day mortality.

Dr. Wechsler: With the exception of people who stayed longer?

Dr. Walther: Obviously.

Dr. Wechsler: Okay. The aortic-valve area calculation interests me. You got about roughly 1.5. I am assuming that was an effective orifice area measured dynamically. And the valves you put in were oversized, they were 26 mm valves. So if you do the calculation at least on the basis of geometric orifice area, it would seem that the valve area should be a lot larger. How do you explain that discrepancy?

Dr. Walther: It is difficult to say. It is the continuing equation that we are using from the echo and, of course, the flow velocity in the left outflow tract and across the valve in the PV and CV Doppler are the parameters you record, and then you record the diameter of the outflow tract and calculate it by the specific formula.
What we do not have is short-axis TOE measurements during follow-up before discharge to do a planimetric orifice area, which could eventually be slightly higher. But, on the other hand, what we have to keep in mind is the annulus was only 22.6 mm in this study, there is still the native calcified leaflets, and some of the valves have a kind of shaped form once they are implanted. So there may be still some minor narrowing. But overall there is no real haemodynamic burden to the ventricle anymore because the gradients are much, much lower than for conventional stented xenografts.

**Dr P. Kappetein** (Rotterdam, The Netherlands): What interests me is what is the technical learning curve and what is due to the fact that you now know better which patients to select for this procedure. Looking at the two Kaplan–Meier curves, I see that patients die until day 120 on your lower curve. So most probably they do not die due to technical aspects of the procedure but more likely due to the co-morbidities of the patient. After that you see more or less a plateauing of the two curves. So, what have you learned during the last three years? Do you now select patients differently or do you perform the procedure differently compared to your earlier experience?

**Dr Walther**: Well, first of all, it is, of course, important to mention that there is still some mortality and I think it is due to the underlying co-morbidities. Regarding the technically related morbidity, this will occur within the first 30 days.

What did we learn? Well, you see that the risk profile in the upper curve is still as high; the STS is slightly lower but the EuroSCORE is slightly higher. The same patients are being included according to the position paper that has been presented in an earlier presentation right here.

We are not selecting our patients. So if there is a very tricky patient, we would not say we don’t treat you. We just have to be aware of that. And I think the technical learning is, for example, the new imaging or the whole team is better aware of problems, or poor ejection fraction so we give some amiodarone beforehand to prevent some persistent arrhythmia after valve implantation, because we know in a poor ventricle during rapid pacing, if this is a bit longer than usual, which can happen, then the pressure can drop. Or what you saw on Saturday in the live case. You saw me knocking on the loader and there was some air. Air can be entrapped if you bring in the valve fast. I was probably not able to get all the air out, so we probably brought some air bubbles in, which you could see on echo, and that is why we had the drop in pressure. Fortunately, that was solved, the patient is fine, was extubated. But there are lots of little things.

And the other thing is if you see us working in Leipzig, we still work with the same team. Same cardiologist, only two, same surgeon, we have trained three others, but it is the same key team always. And even if we are just two surgeons at the table, no problem. We try to see as many cases, if the surgeon just jumps in for five minutes during the critical period. My fellow can prepare everything but we are together, several people decide, and I think learning from several eyes and what everyone sees will help to have a better outcome.

**Dr Kappetein**: Regarding the 30-day mortality I can understand that technical aspects play a role and you have improved your technique, but I still see these curves going down after day 30. A EuroSCORE or an STS score may give us some indication that the profile is more or less the same, but there are also variables that are not captured in the EuroSCORE and STS score. So I think it is important if you could give us some hints which patients we should not treat with percutaneous heart valves?

**Dr Walther**: If you look at the cause of death during follow-up at up to one year, there are, of course, some cardiac problems: there is heart failure and arrhythmias and one only with myocardial infarction, but there is this larger bunch of patients who have some respiratory problems if they acquire pneumonia. This is after three months, you see. This is a mean of 93 days post implant in six patients. So respiratory problems can be a reason for some mortality. And then of course there are others like renal problems or abdominal complications that can occur. It is difficult to really filter that out, but we have to look into those subgroups.

**Dr O. Wendler** (London, UK): I would like to make one comment. It is, of course, quite obvious that we have a group of patients where we miss that they will not benefit from this procedure although they have made a successful implantation. I think that is recognized widely that maybe some kind of geriatric or frailty score needs to come into the equation. That is the reason why for future trials, we have now a six-minute walk test as some kind of assessment of the muscular condition of the patients in addition to the factors we have analyzed previously, and that will maybe help to identify this group of patients better than in the past.

**Dr Walther**: You are definitely right, Olaf, that additional scoring is important but, on the other hand, sometimes, as Dr Enkner earlier mentioned, a bit of gut feeling is still around. You can treat a patient with a EuroSCORE of 80 with a high risk, but you look at the patient, he is willing to undergo this to improve his dyspnea and his circulatory function, and there are others who are lying there very sick. All of you know these slides from Mike Mack with the eyeball test, and that is still a bit valid, but we of course need to have better screening in the future.