Transapical aortic valve implantation using a new self-expandable bioprosthesis (ACURATE TA™): 6-month outcomes†

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Abstract

OBJECTIVES: The ACURATE TA™ Aortic Bioprosthesis and Delivery System (Symetis S.A., Ecublens, Switzerland) is a new transcatheter aortic valve designed for transapical implantation. The six-month results from the completed first-in-man study are reported.

METHODS: The Symetis ACURATE TA™ is composed of a porcine biological tissue valve attached to a self-expandable nitinol stent. It allows for anatomical orientation and facilitates intuitive implantation providing tactile feedback. Since November 2009, a total of 40 high-risk elderly patients have been treated.

RESULTS: The mean age of enrolled patients was 83.2 ± 4.0; 60.0% were female, with a mean logistic EuroSCORE of 21.2 ± 10.8% and a mean Society of Thoracic Surgeons (STS) score of 9.0 ± 4.7%. All implants were delivered successfully in the intra-annular and subcoronary position. One patient was converted to conventional surgery due to coronary impingement (after valve-in-valve implantation). One additional patient received valve-in-valve treatment (SAPIEN THV TA™). Five patients expired within 30 days and two additional patients expired during the 6-month follow-up due to non-valve-related causes resulting in a mid-term survival rate of 82.5%. Two patients suffered a stroke and another three required new onset pacemaker implantation. The mean aortic gradient significantly improved and remained stable throughout the follow-up (baseline: 51.9 ± 14.3 mmHg, 30 days: 12.3 ± 5.1 mmHg, 6 months: 11.9 ± 5.8 mmHg). At the 6-month follow-up, 96.7% of patients demonstrated either none/trace or mild (1+/4) paravalvular leakage only. According to the Valve Academic Research Council the device’s success rate was 92.5%, with a 30-day safety profile of 25%.

CONCLUSIONS: At the 6-month follow-up, the ACURATE TA™ device showed stable valve function with low rates of paravalvular leakages. The cohort of high-risk patients demonstrated good clinical outcomes and 6-month survival.

Keywords: Aortic valve implantation • Minimally invasive • Transapical

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has evolved into a routine procedure at specialized centres treating high-risk elderly patients who are not considered surgical candidates. At present, two devices are approved in Europe for TAVI: the self-expanding CoreValve™ (Medtronic, USA) prosthesis which allows for retrograde transfemoral (TF), or alternatively, transsubclavian/transapical implantation [1]. For the antegrade transapical (TA) approach, the SAPIEN™ (Edwards Lifesciences, USA) device is the only commercially available prosthesis [2]. Both approved devices have demonstrated good outcomes but several issues still have room for improvement: occurrence of paravalvular leak, requirement for new pacemaker implantation, learning curve and the partially limited availability of prosthesis sizes to treat patients with either small or large aortic annulus diameters. Several new TAVI devices are under development for both the retrograde TF and the antegrade TA approaches. Such new developments are of importance to further stimulate research and developments in the field of TAVI for the benefit of future patients.

We herein report a 6-month clinical follow-up using a newly developed transcatheter aortic valve system designed for antegrade TA implantation. The ACURATE TA™ Aortic Bioprosthesis (Symetis S.A.) is based on a self-expanding nitinol stent design. The device allows for a relatively simple and intuitive implantation technique with tactile feedback. The prosthesis was evaluated in Germany within a first-in-man (FIM) trial.

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METHODS

Patients

A total of 40 elderly high-risk patients with severe aortic stenosis (AS) were treated with the ACURATE TA™ from November 2009 until August 2010. The so-called FIM trial was conducted at five German centres. Major inclusion criteria were older age (>75 years) in addition to a high-risk profile (additive EuroSCORE >9) and a severe aortic valve stenosis with a mean gradient >40 mmHg. The mean age of enrolled patients was 83.2 ± 4.0 (74–90) years and 60.0% were female. The baseline mean Logistic EuroSCORE and Society of Thoracic Surgeons score were 21.2 ± 10.8 and 9.0 ± 4.7%, respectively (Table 1). All patients presented as New York Heart Association (NYHA) class III or IV. Clinical decision-making to include the individual patient in the trial was made within an interdisciplinary Heart Team after discussing all available options, including conventional surgery, with the patient. The study protocol was approved by local ethics committees and all patients provided informed consent.

Symetis ACURATE TA™

The ACURATE TA™ is shown in Fig. 1. The device is composed of a surgical-quality porcine tissue valve mounted on a self-expandable nitinol stent which is partially covered by a Polyethylene terephthalate (PET)-skirt. The delivery system has a flexible isodiametric shaft and ergonomic design allowing for a controlled, sheathless, atraumatic and two-step implantation.

Implantation technique

A detailed description of the implantation technique has been published recently [3]. Briefly, the access site is prepared for a TA procedure and a balloon valvuloplasty is performed. The ACURATE TA™ is inserted through the left ventricle and advanced until it is positioned across the native valve. Two radio-opaque markers aid in proper axial positioning and the device can be rotated for commissural alignment (anatomical rotation). The two-step delivery begins with a partial release and final deployment at full release.

Partial release exposes the stabilization arches and the upper crown. The upper crown engages the cusps of the native leaflets and the operator can ‘feel’ the proper placement at the native annulus by gently pulling the ACURATE TA™ down towards the left ventricle. During final release, the prosthesis is slowly unsheathed while gently pulling down towards the left ventricle. The stabilization arches act as a pivot providing further axial alignment. The waist of the ACURATE TA™ captures the native leaflets conforming to the patient’s anatomy. Additionally, the PET-skirt provides a partial ‘seal’ thus reducing the incidence of paravalvular leak.

All implants were performed off-pump with high-quality fluoroscopy under general anaesthesia by an interdisciplinary team involving cardiac surgeons, interventionalists and dedicated cardiac anaesthetists. Transoesophageal echocardiography and a fully primed cardiopulmonary bypass system were available.

Statistics

For statistical analysis, data are 100% complete for safety endpoints. Performance endpoints are determined using available data from existing, evaluable imaging examinations. Continuous variables are expressed as mean plus standard deviation for Gaussian distribution and otherwise median values and ranges only. Categorical data are given in proportions. Survival and freedom from major adverse cardiac and cerebrovascular events (MACCE) curves have been calculated using the Kaplan-Meier method.

Follow-up

According to the study protocol, patients were followed-up at 30 days and 6 months post-implantation with echocardiographic and clinical examinations performed. Clinical safety follow-up

**Table 1:** Preoperative patient demographics (*n* = 40)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>83.2 ± 4.0 (range 74–90)</td>
</tr>
<tr>
<td>Logistic EuroSCORE (%)</td>
<td>21.2 ± 10.8</td>
</tr>
<tr>
<td>STS score (%)</td>
<td>9.0 ± 4.7</td>
</tr>
<tr>
<td>NYHA class III or IV (n/%)</td>
<td>3.3 ± 1.1 or 40/100%</td>
</tr>
<tr>
<td>Redo procedure (n/%)</td>
<td>5/12.5</td>
</tr>
<tr>
<td>Female (n/%)</td>
<td>24/60.0</td>
</tr>
<tr>
<td>Left ventricular EF (%)</td>
<td>56.0 ± 12.9</td>
</tr>
<tr>
<td>Peripheral vascular disease (n/%)</td>
<td>5/12.5</td>
</tr>
<tr>
<td>Carotid artery stenosis (n/%)</td>
<td>6/15.0</td>
</tr>
<tr>
<td>s. p. stroke (n/%)</td>
<td>5/12.5</td>
</tr>
<tr>
<td>Chronic lung disease (n/%)</td>
<td>9/22.5</td>
</tr>
<tr>
<td>Mean aortic gradient (mmHg)</td>
<td>51.9 ± 14.3</td>
</tr>
<tr>
<td>Maximal aortic gradient (mmHg)</td>
<td>83.7 ± 13.5</td>
</tr>
<tr>
<td>Aortic valve opening area (cm²)</td>
<td>0.6 ± 0.2</td>
</tr>
</tbody>
</table>

s. p.: status post. STS: Society of Thoracic Surgeons; EF: Ejection fraction.
was available in all patients; however, three patients did not return for their 30-day echocardiography and two patients had non-evaluable echocardiography (ECHO) performed at rehabilitation centres. Six-month echocardiography was obtained in all patients except for two (patients declined). Follow-up data were collected in a prospective manner. Combined endpoints regarding device success and 30-day safety were defined according to Valve Academic Research Council (VARC) recommendations [4].

RESULTS

Procedure

All devices were delivered and implanted as intended. One patient suffered impingement of the right coronary ostium after valve-in-valve implantation (SAPIEN THV TA™) due to initial paravalvular leak and was converted subsequently to conventional surgery but died in the further postoperative course due to right heart failure. One additional patient received a valve-in-valve (SAPIEN THV TA™). In this case, rebalooning was performed because the initial paravalvular leakage was >2+. Unfortunately, this caused a central leakage due to insufficient pacing during balloon inflation. All other implantations were uneventful. One patient required additional felt-supported stitches at the apex due to initial bleeding. In 17 patients, rebalooning was performed to seal an initial paravalvular leakage. Two patients each suffered a stroke (one intraprocedural, one secondary) and three required new onset pacemaker implantation.

30-day follow-up

Within 30 days post-procedure, five patients expired. A summary of death is shown in Table 2. Echocardiography revealed a mean transvalvular gradient of 12.5 ± 5 mmHg (Fig. 2). None or mild paravalvular leakage was present in 96.5% (n = 28) and moderate leakage in 3.4%, or one patient. No patients exhibited a paravalvular leakage >2+ (Fig. 3). Furthermore, patients demonstrated significant clinical improvement compared with baseline values with 80% of followed patients presenting in either NYHA class I or II (Fig. 4).

Composite endpoint according to VARC (30 days)

According to VARC definitions the device success rate was 92.5% (by definition unsuccessful n = 3: valve-in-valve in two, moderate leakage in one). Combined safety endpoint at 30 days was matched in 10 of 40 (25%) of patients, thus 75% of the patients did not suffer any such event. Detailed description of the 30 day combined safety endpoint is listed in Table 3.

6-month follow-up

In between the 30-day and 6-month follow-ups, two patients died due to non-valve-related reasons (Table 2) resulting in a total...
6-month survival rate of 82.5% (Fig. 5A). Six-month freedom from MACCE was 75.0% (Fig. 5B). No patients had undergone any further valve-related intervention since the procedure. Endocarditis, thrombosis or valve degeneration was not observed. No patients exhibited clinically apparent haemolysis and delayed valve embolization or dislodgement was not observed in any patient. Further implantation of a new pacemaker (except in the three patients postoperatively) was not required during follow-up.

All patients demonstrated continuing clinical improvement, with 90.0% of patients exhibiting either NYHA class I or II at the 6-month follow-up.

Echocardiography at 6 months revealed stable low transvalvular mean aortic gradients. In addition, the rate of relevant paravalvular leakage were low, with 96.7% of patients demonstrating either none/trivial or mild (1+/4) paravalvular leakage and 3.3%, or one patient demonstrating moderate (2+/4) paravalvular leakage only. There are no patients with a >2+/4 leakage.

## DISCUSSION

TAVI has evolved into an accepted treatment alternative for high-risk elderly patients with severe AS. Recently, improved survival for TAVI compared with medical therapy has been proven (PARTNER trial cohort B) in high-risk patients not suitable for conventional aortic valve replacement [5]. In addition, TAVI appears to result in at least as good an outcome (non-inferiority) after conventional surgical aortic valve replacement in a high-risk population (PARTNER trial cohort A) [6]. However, only two marketed devices (CoreValve™ and SAPIEN THV™) are currently available to treat these patients using a retrograde (TF) approach. For the TA approach, the only device commercially available today is the SAPIEN THV™. Given the rapid growth of TAVI performed, and the predicted future potential of the procedure, it is obvious that the availability of different devices will lead to improved solutions for the patients in the future. This might eventually allow selection of the most appropriate device for an individual patient. The Symetis ACURATE TA™ was designed to provide an alternative for TA implantation. Key features are its use of a non-coronary leaflet porcine tissue valve within a self-expandable nitinol frame (similar to a surgical tissue bioprosthesis) and its unique two-step implantation technique facilitating relatively simple intuitive positioning with tactile feedback. Its simplified positioning technique could have an impact on the learning curve that must be overcome with both currently marketed devices [7-9].

The outcome achieved using the ACURATE TA™ in this FIM trial is promising when compared with data from other European TAVI trials and registries of the two commercially available devices. The observed 30-day mortality and stroke rates are in the expected range compared with what is reported in the European literature today. Even more importantly, the 6-month survival after implantation of this new device, that by definition includes a certain learning curve, results in a similar 6-month survival compared with the well-established marketed TAVI devices [10, 11].

The observed rate of new pacemaker requirement after ACURATE TA™ implantation (7.5%) is similar to rates reported after implantation with the SAPIEN™ prosthesis [2] and compares very favourably with the known high rate of pacemakers required after CoreValve™ implantation [12, 13].

A still unsolved issue associated with TAVI is the rate of paravalvular leakage. While there is general consensus that mild (1+/4) leakage is well tolerated, the impact of moderate (2+/4) and more severe leakage (>2+/4) is still under debate. The rate of >1+/4 (mild) leakage reported after either SAPIEN THV™ or CoreValve™ implantation is variable and ranges between 7 and 20% [14-17]. Recently, data from a German TAVI registry (mostly TF CoreValve™ implantations) became available. The group observed >1+/4 paravalvular leakage in 17.2% of patients and were able to demonstrate a significant impact on in-hospital mortality (odds ratio 2.43; 1.22-4.85) by multi-variate analysis [18]. This report highlights the importance of avoiding residual paravalvular leakage after TAVI. In this context, the observed rate of >1+ leakage after treatment using the new ACURATE TA™ compares favourably with only 7.7% (none >2+/4) assessed immediately post-procedure [3]. At the 6-month follow-up, a trend...
towards even less leakage was observed with 96.7% of patients demonstrating either none/trace or 1+/4 paravalvular leakage only. If some leakage truly disappeared during the 6-month follow-up or was just not visible by TTE in contrast to post-procedural angiographic evaluation remains speculative. However, paravalvular leakage remained stable and appeared to improve over time as it has also been observed with both the approved devices on the market [11, 19]. As already mentioned, the observed rate of residual paravalvular leakage was extremely low. We believe that this is due to the specific design of the stent including the covered section at the annular level in addition to the implantation technique where calcifications are ‘pulled down’ into the annular plane which might further help to seal for leakages. However, in 42.5% of patients additional post-dilatation has been performed to achieve these outstanding results. In our opinion, frequent rebalooning was necessary for the following reasons. Initial radial forces of the ACURATE TA™ are probably not as high as those of the balloon-expandable SAPIEN™ device. In addition, valvuloplasty has been performed cautiously during this initial series. After having gained more experience, we now suggest relatively ‘aggressive’ pre-balooning which seems to work very well in regard to the necessity for further post-dilatation. Finally, we are convinced that any residual leakage >1+ should rarely be left untreated given the known impact on long-term outcome [18]. One could argue that post-dilatation is an additional risk factor or might have an impact on long-term durability. However, in our experience, the only drawback of rebalooning is the requirement for another period of rapid pacing, which is unproblematic except in patients with severely reduced ventricular function. A potential correlation of reduced durability due to a potentially detrimental effect of a balloon within the bioprosthetic leaflets is an interesting hypothesis that cannot be further evaluated at present. However, all patients receiving a SAPIEN™ prosthesis would then experience this kind of effect even without post-implantation rebalooning.

CONCLUSION

In this FIM trial, we have observed promising mid-term results using the ACURATE TA™, designed for TA implantation. Survival, rate of device success and combined 30-day safety endpoints (according to VARC) including stroke rates are comparable with European data reported for both currently available TAVI devices. Requirement for a new onset pacemaker implantation is within an acceptable range comparable with SAPIEN™ data. Functional outcomes are good with low and stable transvalvular gradient and most importantly, vary low rate of relevant paravalvular leakage leading to significant clinical improvement of patients. With its unique ease of use and promising 6-month follow-up results, the ACURATE TA™ will be an alternative TA TAVI treatment for patients with severe AS once CE mark approval is achieved.

Funding

The ACURATE TA FIM trial was sponsored by Symetis (Switzerland).

Conflict of interest: none declared.

REFERENCES

APPENDIX. CONFERENCE DISCUSSION

Dr N.M. Van Mieghem (Rotterdam, Netherlands): I have one question. What is the size of the delivery system, of the catheter?

Dr Kempfert: The size of the delivery catheter is comparable to a 28-Fr sheath system. So the outer diameter is around 31.

Dr Van Mieghem: And I also discussed the JenaValve this morning. Do you have data on myocardial necrosis?

Dr Kempfert: No. But, of course, as with all the transapical implants, we see a slight enzyme release after the procedure. We currently have another trial underway trying to assess that topic especially, but I don’t expect that with the Symetis or the JenaValve compared to a Sapien, there is a true difference in regard to the sheath size. That is what you are asking for, right?

Dr Van Mieghem: Yes. And then, finally, you mentioned the paravalvular AR, but you did a post-dilatation in 40% of the cases.

Dr Kempfert: Yes.

Dr Van Mieghem: Are you afraid of that for long-term durability?

Dr Kempfert: That is actually a good question. You mean if the post-dilatation might have an influence on the long-term durability. I think that as long as you have sufficient rapid pacing, so a really stable balloon, then I don’t think that this might cause any relevant leaflet damage. You also have to take into account with the Sapien, for instance, or any other potential balloon-expandable valves, you will always have a balloon blown up in the valve, so a kind of mandatory post-dilatation in comparison to the self-expandable nitinol design?

Dr O. Wendler (London, UK): Do you think that the sheathless approach is in any way helpful? Do you find it easier to manage the patient without going in and out with different catheters and wires?

Dr Kempfert: I would not necessarily say that it is easier, but it reduces the diameter of the ventricular access. Despite that it is always said that for the apical access, sheath diameter does not play an important role, I am not so sure about that. I still think that the lower the profile, the safer the procedure. This is why we just abandoned the sheaths.

Dr A. Diegeler (Bad Neustadt, Germany): Do you think that the multistep delivery, the rotation and retraction, is an additional risk for strokes?

Dr Kempfert: We have asked that ourselves as we had two strokes in 40 patients, but this is, again, something that we would need to have more data on. But I have the feeling that the actual implantation of the valve might not be the major factor for stroke. We have seen it also in the other presentation in regard to balloon valvuloplasty. Even with an isolated valvuloplasty, you might see an MRI lesion. The critical point is that we still don’t know if there is really a link between the onset of an MRI lesion or a transcranial Doppler signal and a true clinical neurological event. These are two pairs of shoes, I assume.

Dr Wendler: On the other hand, do you feel that due to the fact that you are able to rotate the valve and implant it in an anatomical position, you are more comfortable in terms of reducing the risk of coronary complications?

Dr Kempfert: This is also an issue that is under debate. We have also implanted the Sapien with anatomical rotation in a few patients. Of course, you could argue that for some reason nature put the commissures where they are. So if you can mimic that, what is wrong about that? On the other hand, I fully agree it also enhances the complexity of the actual procedure a little bit. But the idea behind the anatomical rotation concept is to stay away from the coronary ostia in regard to the device commissures. To answer whether this will have a real clinical impact, usually you would need to have a randomized trial. So I don’t know. But as it is not so hard to obtain with this device, it is worth the attempt. The device commissure is clearly visible on the fluoros, so it takes only a few seconds, so why not do it if it is feasible and safe.

Dr N. Moat (London, UK): Just a comment. I think you made a bit of a point of saying that the six-month mortality was comparable with other devices. The meta-analysis of the European registries that has been presented a couple of times had a one-year mortality of about 81%, which compares with the 81% that you are reporting at six months. I am not suggesting that this device is worse, but I think you need to be a little cautious about making such statements.

Just to finish the session, I am going to ask you a philosophical question. I think the bar has been set very high by Edwards Sapien and Medtronic CoreValve. How do you think these new devices should be brought into the marketplace, given the excellent results those first-generation devices have achieved?

Dr Kempfert: It is more a marketing question, actually. You are absolutely right that the bar is very high right now, but those new devices, first of all, will be just an alternative. At present, as we all know, we have only one device for the transapical access. By definition, this is something that is not good, if there is only one company involved. In addition, I think that especially in regard to the learning curve, it seems that with the Symetis device the positioning might be a little bit easier to accomplish as with the Sapien. This might not be a major factor for these TAVI centres that have done hundreds of valves, but it might have a benefit, especially for the small-volume centres. So eventually we might come to a certain point where we can choose the most appropriate valve type based on the individual anatomy of the patient. This will take, of course, a few years, but this is actually what we do with regular surgical tissue valves, right?

Dr Moat: That is a very good answer.