INTRODUCTION

In the past few years, the number of transcatheter aortic valve implantation (TAVI) procedures has exponentially increased [1]. The majority of patients receive TAVI using either an antegrade transapical (TA) or a retrograde transfemoral (TF) access. In parallel to increasing numbers, TAVI procedures have become more and more standardized. Due to the fact that there are no randomized clinical trials, there is no evidence indicating the superiority of a TF or a TA approach. Despite this, many clinicians believe that the TF approach may be less invasive and thus, apply a TF first strategy leading to a bias in patient selection.

The TF approach, however, is limited in patients with peripheral vascular disease blocking a femoral–iliac access and may be associated with a higher incidence of vascular complications compared with the TA approach [2, 3]. In addition, some recent publications have shown a significant impact of severe vascular complications on patient outcomes [4]. In contrast, the TA approach provides a safe and reproducible access, which can be performed in nearly every patient. Large multicenter trials have shown an incidence of <1% of access-related complications with TA-AVI [5, 6]. The goals of any TA access and closure device are to reduce the learning curve and standardize TA access and closure without compromising safety. In a future step, a percutaneous TA approach may then become a reality.

Therefore, the aim of this first-in-man trial was to evaluate the technical and clinical performance of the new APICA ASC™ device to facilitate and standardize the TA approach.
MATERIALS AND METHODS

The APICA ASC™ device

The ASC™ device (Apica Cardiovascular Limited, Galway, Ireland) is a pre-mounted access stabilization and closure system to facilitate and standardize the TA delivery of heart valves. The Apica ASC™ system consists of three parts: an introducer, a left ventricular low-profile titanium coil and a closure cap (Fig. 1). The introducer system and titanium coil are one part and are delivered over a super-stiff guidewire and achieve left ventricular access by rotating the titanium coils into the myocardium with the Ascendra II or II plus™ sheath (24f) and dilator inside. The titanium coil provides secure attachment and myocardial compression around the sheath, providing access and stabilization without peri-sheath bleeding while performing beating heart procedures. Following the procedure, the closure cap is introduced through the ASC™ introducer system and delivered into the titanium coil for final epicardial sealing of the apical access site. The device is designed such that it can accommodate different heart valve’ delivery systems and access sheaths.

Patients

From May until July 2012, a total of 11 high-risk elderly patients suffering from severe isolated aortic valve stenosis were scheduled for TA-TAVI by our interdisciplinary Heart Team and were included into the study after gaining the patients informed consent. The study protocol was approved by the local ethics committee (Reference: III/1/woe/opi/FF 4/2012) by the German regulatory body 'Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)' (Reference: CIV-12-01-003662). Any patients suffering from chronic renal insufficiency requiring chronic dialysis, severe reduced left ventricular function (ejection fraction <30%), myocardial infarction <1 month prior to scheduled TAVI, stroke or transient ischaemic attack <6 months prior to scheduled TAVI or a thin (<10 mm by CT) left ventricular wall were excluded from the trial.

Procedure

Exposure and puncture of the left ventricular apex were performed in the usual manner [7]. In all cases, the Edwards Ascendra II™ or Ascendra II plus™ delivery system and the Edwards SAPIEN XT™ valve were used. The Edwards introducer sheath and dilator were prepared and pre-mounted into the APICA ASC™ device (Fig. 2). All procedures were performed under heparinization of 101 IU/kg, aiming an activated clotting time of 300 s. After positioning of the super-stiff guidewire, the introducer sheath and dilator were inserted over the wire into the left ventricle by rotating the titanium coil like a corkscrew against the epicardial surface for two and a quarter turns (Fig. 3). After insertion, the externalized parts of the system had good contact with the epicardium. After removal of the dilator of the Ascenda™ sheath, the routine TA-TAVI procedure was performed through the ASC™ device in a routine manner, followed by functional valve assessment (Fig. 4). Then the super-stiff
guidewire and the Ascendra™ sheath were removed, and the closure cap was inserted through the ASC™ introducer system to achieve final closure of the access site. Finally, the closure cap and introducer system were disengaged and removed (Fig. 5). The pericardium was partially closed in all patients. Before wound closure, the function of the implant was assessed and a drainage was inserted. Total periprocedural blood loss and procedure times were documented. Postoperatively, all patients received aspirin 100 mg, clopidogrel 75 mg for 3 months and low molecular heparin until full mobilization.

Post-procedural examination

The primary endpoint of this study was device safety evidenced by the absence of acute bleeding or development of pseudoaneurysm. Post-procedural blood loss was documented by drainage volume. Secondary endpoints were any impairment in left ventricular function and potential occurrence of new wall motion disturbances as assessed by echocardiography. Furthermore, patients received 24 h Holter electrocardiogram (ECG) on postoperative day (POD) 4/5 for the documentation of potential life-threatening arrhythmias. Along with the usual blood chemistry, creatine kinase (CK)/creatin kinase MB (CK-MB) and Troponin were documented at baseline, post-procedurally, on POD 1, 2, 4 and before discharge. Follow-up visits in regard to general health examination and echocardiographic assessment of left ventricular function and valve performance were performed at 30 days after the procedures. Subsequent follow-up visits are scheduled for 90 days, 6 months and 1 year.

RESULTS

A total of 11 high-risk patients (age: 82.8 ± 0.7; females: 7; EuroSCORE I: 27.8 ± 16.7; EuroSCORE II: 6.6 ± 5.0 and The Society of Thoracic Surgeons (STS) score: 5.9 ± 2.7%) were consented. Demographic data are summarized in Table 1. One patient was excluded after apical exposure due to the presence of deep epicardial fatty tissue as stated in the study protocol. This patient had expected sealing in all patients without the aid of fluoroscopy. Additionally, the ASC™ device showed a stable device without evidence of any residual insufficiency in 7 patients. In none of the patients was any moderate or severe aortic insufficiency observed. Subsequently, the closure cap was delivered through the ASC™ introducer sheath into the access coil to achieve complete haemostasis in all patients. No residual bleeding was observed in any patient after administration of protamine. Total blood loss during the procedure was 118.5 ± 57.7 ml. Total procedure time was 60.4 ± 12.6 min. All patients were extubated directly after the procedure, on the table. All patients were referred to intermediate care after the procedure. All drainages were removed within 1.4 ± 0.7 days. Total blood loss until removal of the drainage was 541 ± 400.1 ml.

Blood chemistry revealed an expected increase in CK/CK-MB and Troponin within first 24 h (P < 0.001). Before discharge, myocardial enzymes showed a significant decrease (P < 0.05) in all patients (Fig. 6A–C). Discharge echocardiography revealed a slight, but not significant increase in left ventricular ejection fraction without an incidence of new wall motion disturbances in all patients (P = 0.140). A mild paravalvular aortic regurgitation was observed in 3 patients and a moderate aortic regurgitation in 1. The mean aortic gradient was 13.3 ± 10.2 mmHg. Twenty-four-hour ECG Holter was performed in 8 patients and could not detect any life-threatening arrhythmia on POD 4/5. One patient suffered from non-device-related pericardial effusion, which could be removed after 12 h without any further blood loss. Two patients suffered from secondary, delayed and minor transoesophageal echocardiography revealed a trivial paravalvular insufficiency in 7 patients. In none of the patients was any moderate or severe aortic insufficiency observed. Subsequently, the closure cap was delivered through the ASC™ introducer sheath into the access coil to achieve complete haemostasis in all patients. No residual bleeding was observed in any patient after administration of protamine. Total blood loss during the procedure was 118.5 ± 57.7 ml. Total procedure time was 60.4 ± 12.6 min. All patients were extubated directly after the procedure, on the table. All patients were referred to intermediate care after the procedure. All drainages were removed within 1.4 ± 0.7 days. Total blood loss until removal of the drainage was 541 ± 400.1 ml.

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### Table 1: Preoperative patient demographics

<table>
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<tr>
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<tr>
<td>Age (years)</td>
<td>82.8 ± 0.7 (range 74-87)</td>
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<tr>
<td>Logistic EuroSCORE (%)</td>
<td>27.8 ± 16.7</td>
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<tr>
<td>EuroSCORE II (%)</td>
<td>6.6 ± 5.0</td>
</tr>
<tr>
<td>STS score (%)</td>
<td>5.9 ± 2.7</td>
</tr>
<tr>
<td>New York Heart Association class</td>
<td>3.3 ± 0.1</td>
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<tr>
<td>Redo procedure (n%)</td>
<td>3/27.2</td>
</tr>
<tr>
<td>Female (n%)</td>
<td>7/63.6</td>
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<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>54.8 ± 7.6</td>
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<tr>
<td>Peripheral vascular disease (n%)</td>
<td>4/36.3</td>
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<tr>
<td>Carotid artery stenosis (n%)</td>
<td>3/27.2</td>
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<tr>
<td>Status post stroke (n%)</td>
<td>1/9.0</td>
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<tr>
<td>Chronic lung disease (n%)</td>
<td>1/9.0</td>
</tr>
<tr>
<td>Status post pacemaker implantation</td>
<td>2/18.8</td>
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<td>Mitral valve insufficiency &gt; I° (n%)</td>
<td>0/0</td>
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Figure 5: (A) Final result after disengagement of the implant. (B) Final result under fluoroscopy.
stroke most likely caused by new onset atrial fibrillation. Both patients were referred to a stroke unit immediately and showed a good functional recovery. Ventricular thrombus or pseudoaneurysm could be excluded by transoesophageal echocardiography and MRI scan in these 2 patients. Post-procedural data are summarized in Table 2.

Thirty-day follow-up was completed in all patients. All patients were alive at 30 days. Echocardiography revealed no changes in left ventricular function when compared with discharge in all patients. No wall motion disturbances could be observed in any patient. Left ventricular function showed a slight increase in comparison with discharge (57.6 ± 6.6 vs 60.0 ± 7.7%), without reaching statistical significance (P = 0.09).

DISCUSSION

The majority of TAVI procedures are being performed using a retrograde TF or/and antegrade TA approach. Despite the fact that there is no scientific evidence of the TF or TA approach being superior, many centres follow a TF first strategy. A potential reason might be that the TA approach is assessed to be more invasive than the TF approach. In contrast, it is based on evidence that TF-AVI is related to a high incidence of vascular complications during TF-AVI, which is reported to be between 8 and 30% in the current literature [2-4]. More importantly, a recent publication still identified major vascular complications, defined by the criteria of the Valve Academic Research Consortium (VARC), as a predictor of an increase in 30-day and in-hospital mortalities [4, 8]. Therefore, the presence of peripheral vascular disease or significant stenosis of femoral or iliac arteries should be considered real contraindications for the TF approach.

The TA access per se offers multiple advantages. One of the main advantages of the TA approach is the independence of the sheath diameter. There are no limitations, and newer valve generations, even if they require slightly larger diameters, but provide beneficial solutions to minimize the risk of paravalvular leakage, will be helpful for our patients [9]. In addition, the vascular complication rate after TA-AVI is reported <1% [3, 5, 10]. Even apical access-related complications, for example, bleeding from the puncture side or pericardial effusion have recently been reported to be <1% in the PREVAIL trial or 2.4% in the SOURCE registry, both multicentre European data [5, 6].

Recently, we could prove concept of a new apical access, stabilization and closure device in an experimental model. The aim of this study was to evaluate this new apical access, stabilization and closure (ASC™) device in a human first-in-man setting [11]. The system relies on a sealing mechanism using an initial titanium coil to compress tissue followed by a final titanium closure cap. It is compatible with several current TAVI devices from different companies. In this trial, the Edwards Ascendra II™ and Ascendra II plus™ introducer system were used. In all patients, the ASC™ device could be implanted successfully and provided a blood-tight seal during the whole procedure. The TA-AVI procedure could be successfully performed through the ASC™ device. The closure cap provided a sufficient sealing of the device. No relevant intraprocedural bleeding occurred. Handling of the device was simple, with no interference with the Edwards Ascendra™ system being experienced. In all cases, patients could be extubated directly after the procedure and could be referred to the intermediate care unit. Therefore, the overall use of the ASC™ system was safe and successful. It provided standardized access and closure and was easy to handle.

### Table 2: Post-procedural data

<table>
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<tr>
<td>30-day mortality rate (n/%)</td>
<td>0/0</td>
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<tr>
<td>New pacemaker implantation (n/%)</td>
<td>0/0</td>
</tr>
<tr>
<td>Stroke rate (n/%)</td>
<td>2/20</td>
</tr>
<tr>
<td>Temporary haemodialysis (n/%)</td>
<td>1/10</td>
</tr>
<tr>
<td>Access-related complications (n/%)</td>
<td>1/10</td>
</tr>
<tr>
<td>(rethoracotomy, major bleeding)</td>
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Figure 6: (A) CK values during hospital stay, (B) CK-MB values during hospital stay and (C) Troponin HS values during hospital stay.
Post-procedural echocardiography actually revealed a slight, not significant, increase in left ventricular function when compared with baseline. This is well within the expectations of patients receiving TA-AVI. Even though a significant increase in left ventricular function can be expected after the treatment of aortic stenosis, myocardial fibrosis as well as the duration of the disease may also contribute. In none of the cases, the presence of pseudoaneurysm or wall motion disturbances was observed. The initial concerns that the permanent titanium implant might have an impact on left ventricular function could not be proven. As such, the system has proved to be very safe and easy to apply and provides excellent short-term results. The initial significant increase in CK/CK-MB after the procedure is usual and also seen after the suture-based TA approach. Even after TF-AVI, a significant increase in these values is documented, which could most likely be explained by a remodelling of the hypertrophic cardiac muscle after intervention [12, 13].

During the trial, 2 patients suffered from delayed stroke. In both patients, new onset atrial fibrillation could be identified retrospectively. Frankly, anticoagulation had not been adjusted accordingly. Stroke is an often-discussed issue after TAVI, and some also rely on a permanent implant, while others are purely suture based [17]. A potential advantage of the ASC device is the financial relationship with Apica Cardiovascular Limited.

REFERENCES


Conflict of interest: Vinod Thourani is co-founder of and has a financial relationship with Apica Cardiovascular Limited.
APPENDIX. CONFERENCE DISCUSSION

Dr V.A. Subramanian (New York, NY, USA): This is an important paper in the whole field of facilitated technologies in the TAVI world. I have no conflicts of interest. I guess I am very unbiased because I have no practical clinical experience in TAVI.

Dr Blumenstein and his colleagues have shown that this simple but very ingenious LV closure system has been successful in 10 patients undergoing transapical TAVI, especially in terms of ease of deployment of the system, excellent intra- and peri-procedural haemostasis, major adverse events in a short-term follow-up, and suggest the potential use of this device for other procedures in the world of "bottoms up" approach to the inside of the heart. I have several questions related to the technical aspects of the procedure, device dimensions, and potential long-term complications. Some of these questions may not be answered by the clinical trial but perhaps from the chronic preclinical information you or your senior authors might have. I will ask you one by one so it is easier to answer the questions.

The first question is related to the potential bailout if you have a problem during the procedure, for example, a fragile myocardium, if you have bleeding around the device, what would you do? Would you place additional sutures or would you explant the device or reinsert the device?

Dr Blumenstein: I think the best way is to just let the implant stay in place and put sutures around the device and tie them down and afterwards close the system. This might be the best way to handle this complication.

Dr Subramanian: Obviously you don’t have that in your clinical trial. Have you tested it in the chronic animal studies or acute animal studies?

Dr Blumenstein: Not yet.

Dr Subramanian: What happens if we have to take this device to re-access for some other TAVI procedures inside, for example, valve embolization? How easy is it to re-engage in the base of the coil for stabilization and re-engage the plug and take it out and how complex will an acute re-entry be? Has that been tested in animals?

Dr Blumenstein: We just simulated this in the animal trial, and it was very easy to reattach the system to the coil, and after reattachment of the introducer system, it was very easy to return the closure cap and to reopen the access and to follow the next procedure.

Dr Subramanian: This is an intramyocardial implant and you have one size, and I see you have excluded the people with 10 mm thickness and under. What happens if you have a very huge LV mass, LV thickness? Do you need a different size or will there be a chance, because this device (it is a low device, low height) will be remaining superficially into the myocardium? Is there any device migration potential either in the LV hypertrophy model in the animals or any further clinical experience you might have had?

Dr Blumenstein: Typically, TAVI patients do have hypertrophy of the left ventricle. Insertion of the device into the ventricle is not required. So you just need the stabilization into the myocardium and then you can penetrate the left ventricle through the device. Therefore, it doesn’t depend on the thickness. It has to be thicker than 10 mm, but you don’t need to penetrate the whole ventricle to get into the ventricle.

Dr Subramanian: So you won’t need different sizes for different varying thicknesses?

Dr Blumenstein: No.

Dr Subramanian: The height of the plug is smaller than the height of the coil. It is intramyocardial, a short distance. You still have an entry in the tract and the endocardium. Will there be a potential seepage acutely, some blood to come down into the tract causing a potential nidus? The reason I am asking is that you had two strokes which you assume to be due to atrial arrhythmia. Obviously TEE and MRI scan may not be sensitive enough to detect thin layers of thrombus. So could there be a problem in that space? The second question, and the corollary to that is, would you use a much more vigorous anticoagulation regimen in these patients in the light of the two strokes you had in 10 patients?

Dr Blumenstein: Excuse me. Can you just repeat? I didn’t understand the first sentence.

Dr Subramanian: You do have a height of the coil and then there is a tract which the system goes in. You will have an endocardial entry, and unless the endocardial entry closes very quickly and the myocardium itself closes, there may be some blood seepage. I am not sure; I am asking. Will there be blood seepage, where possibly or potentially a nidus will be there? And I know you said it is atrial fibrillation, but how sure could it be, suggesting that perhaps you may want to have a higher anticoagulation regimen.

Dr Blumenstein: I think there are two important things. The room inside of the coil is filled with myocardium even after the procedure.

Dr Subramanian: So therefore I don’t think there is some kind of hole where you can find thrombus after the procedure. And the second thing is all these strokes we described in the paper were delayed strokes. Therefore I think the typical anticoagulation regimen has to be redesigned for typical TAVI patients.

Dr Subramanian: So basically you are saying the current anticoagulation regimen has to be tuned up. Okay, that is fine for time’s sake. And finally, two very short questions. Have you done any or do you plan to do some LV grams at some point of the study just to see if there is any myocardial staining? And I know you didn’t have a pseudoaneurysm, but a pseudoaneurysm takes a long time. Just to see if there is any myocardial staining in the myocardium somewhere along the tract will give a clue. Are you going to do that?

Dr Blumenstein: We actually performed an MRI scan on one patient, and in this patient we didn’t see any incidence even of pseudoaneurysm or any left ventricular wall motion disturbances.

Dr Subramanian: The last question is chronic re-entry. I hope these patients don’t need any chronic re-entry, younger patients. How solid are you, let’s say one year later or nine months later, that fibrous tissue and everything else is going to be forming and you are going to re-engage this coil stabilization and the plug to take it out? I just left it to the stretch of the imagination, but I would just stick to the current acute entry phase and do it.

Dr Blumenstein: It is a titanium coil, so therefore the fibrosis on this one will not be expected, but in all the chronic animals we can show a potential re-access with the device, but we have to re-evaluate it in humans this way.

Dr G. Lauffer (Vienna, Austria): Do you have any idea about the cost of the device?

Dr Blumenstein: Not yet.

Dr O. Alferi (Milan, Italy): May I ask another question? Are you aware of scientific data showing the reduction of left ventricular ejection fraction with a conventional closure of the apex?

Dr Blumenstein: The idea of the implant is that it relies on the compression. Therefore, in contrast to a suture (the suture is tying the myocardium together and it provides a scar), the system relies on an implant which relies on compression on the myocardium. We also performed an MRI scan on the suture-based technique, and we have seen a bigger scar on suture-based patients than the patients with the Apica implant. So in all the left ventricular angiographies and the echocardiographies there was no incidence of any wall motion disturbances after 30 days and even the patients we have already seen after 90 days. So therefore we don’t think that the device will have an impact on left ventricular function.

Dr Alferi: Yes, but what is the reduction of the ventricular function with the conventional closure of the apex? Do you have some scientific data on that?

Dr Blumenstein: Not yet.

Dr J. Kempfert (Bad Nauheim, Germany): I would like to comment on your question about whether there is any scientific data proving that there is any impact on LV function. I think we have seen also in SOURCE that, unexpectedly, if you discharge patients, you usually do not see a significant increase in ejection fraction despite the implantation of an aortic valve. You would potentially expect that, but you will not see an improvement that early. And if you then compare TF and TA patients, we recently did a trial with only 20 patients, where the TF patients served as a control group to the TA patients. The only difference was the access. We were not able to show any difference between TF and TA in regard to ejection fraction assessed by MRI and echo at discharge. So I actually doubt that there is a negative impact of the transapical approach on LV function.