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STRUCTURAL

Transcatheter Aortic Valve Replacement Using Transaortic Access

Experience From the Multicenter, Multinational, Prospective ROUTE Registry

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ABSTRACT

OBJECTIVES The Registry of the Utilization of the TAo-TAVR approach using the Edwards SAPIEN Valve (ROUTE) was established to assess the effectiveness and safety of the use of transaortic (TAo) access for transcatheter aortic valve replacement (TAVR) procedures (NCT01991431).

BACKGROUND TAVR represents an alternative to surgical valve replacement in high-risk patients. Whereas the transfemoral access route is used commonly as the first-line approach, transapical access is an option for patients not suitable for transfemoral treatment mainly due to anatomic conditions. TAo-TAVR has been shown to be a viable alternative surgical access route; however, only limited data on its effectiveness and safety has been published.

METHODS ROUTE is a multicenter, international, prospective, observational registry; data were collected from 18 centers across Europe starting in February 2013. Patients having severe calcific aortic stenosis were documented if they were scheduled to undergo TAo-TAVR using an Edwards SAPIEN XT or a SAPIEN 3 valve. The primary endpoint was 30-day mortality. Secondary endpoints were intraprocedural or in hospital and 30-day complication rates.

RESULTS A total of 301 patients with a mean age of 81.7 ± 5.9 years and an Society of Thoracic Surgeons score of 9.0 ± 7.6% were included. Valve success was documented in 96.7%. The 30-day mortality was 6.1% (18/293) (procedure-related mortality: 3.1%; 9 of 293). The Valve Academic Research Consortium-2 defined complications included myocardial infarction (1.0%), stroke (1.0%), transient ischemic attack (0.3%), major vascular complications (3.4%), life-threatening bleeding (3.4%), and acute kidney injury (9.5%). In 3.3% of patients, paravalvular regurgitation was classified as moderate or severe (10 of 300). Twenty-six patients (8.8%) required permanent pacemaker implantation.

CONCLUSIONS TAo access for TAVR seems to be a safe alternative to the transapical procedure.
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ABBREVIATIONS AND ACRONYMS

TA = transapical

TAo = transaortic access

TAVR = transcatheter aortic valve replacement

TF = transfemoral

In patients with severe aortic stenosis, unsuitable for open heart surgery, transcatheter aortic valve replacement (TAVR) represents an alternative treatment option (1). Transaortic access (TAo) is an additional access route to transfemoral (TF) or transapical (TA) routes. It is used in patients that are neither suitable for TF access, due to anatomic abnormalities or peripheral vascular disease, nor TA access, due to respiratory disease or decreased left ventricular function (2–7). Initial studies investigating TAo-TAVR have reported ease of access, good visualization, and low risk of hemorrhage, in addition to comparable complication and mortality rates to the other access routes (4,7–9). However, each of the approaches is associated with advantages and disadvantages resulting in different TAVR-related complications (10–14). Because the majority of studies regarding TAo-TAVR using the SAPIEN transcatheter heart valve have been single-center case series and have included relatively low numbers of patients, there is a need to confirm morbidity and mortality outcomes by evaluating a large, multinational population (3,6,9,15).

SEE PAGE 1823

With the aim of meeting this need, the ROUTE (Registry of the Utilization of the TAo-TAVR approach using the Edwards SAPIEN Valve) was established (16). This is a multicenter, international, prospective registry that included patients who received either the SAPIEN XT or the SAPIEN 3 valves (Edwards Lifesciences, Irvine, California) via TAo. The primary aim of the study was to assess overall mortality during a 30-day follow-up. Further, procedural characteristics, complications, and TAVR-related mortality were investigated.

METHODS

STUDY DESIGN AND SITE SELECTION. ROUTE is a multicenter, multinational, prospective, observational registry (NCT01991431) (16). Patients were enrolled consecutively at 18 centers across Europe (France, Italy, Netherlands, the United Kingdom, Poland, Finland, Denmark, Norway, Germany, and Austria) from February 2013 through February 2015. Each site was required to have prior experience with TAo-TAVR using the SAPIEN valve (minimum 5 implantations). All patients included in the registry provided written informed consent, and ethical approval was obtained from the relevant committee at each site.

PATIENTS. Patients with severe calcific aortic stenosis were included if they were scheduled to undergo TAo-TAVR using an Edwards SAPIEN XT or a SAPIEN 3 valve (16). Patients were excluded if they had congenital unicuspid or bicuspid aortic valves; evidence of intracardiac mass, thrombus, vegetation, active infection, or endocarditis; an inability to tolerate anticoagulation or antiplatelet agents; or excessive calcification of the access site. Patients who were scheduled to receive an additional procedure besides TAVR, such as coronary artery bypass grafting, were also excluded.

DOCUMENTATION AND ENDPOINTS. At admission, a full cardiac history was taken, and comorbidities were recorded. Further data were collected at the time of the TAVR procedure, at discharge, and at 30 days after the procedure. Complication rates were defined according to the Valve Academic Research Consortium-2 criteria (17). The information was entered into an electronic database, at which point it was checked for plausibility and completeness (16). The primary endpoint was overall 30-day mortality. Secondary endpoints were intraprocedural, in-hospital, and 30-day complication rates.

STATISTICS. The required sample size was calculated on the basis of an overall mortality of 7.1% at 30 days, an estimate which relied on unpublished data from the principal investigators (16). This gave an initial required population of 200 patients. From February 2014, the newly approved SAPIEN 3 valve could also be used. Therefore, in June 2014, the study was expanded to include a further 100 patients.

Descriptive statistics are provided for all evaluable data. Categorical variables are presented as absolute

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values and percentages. Continuous variables are given as mean ± SD. Change in aortic valve peak and mean gradient between pre-procedure and post-procedure were compared using analysis of variance. Centers and countries were included as random factors in the model. The risk for overall 30-day mortality was calculated using a logistic model, including age, left ventricular ejection fraction, presence of syncope or dizziness, prior pacemaker implantation, hypertension, peripheral artery disease, pulmonary hypertension, TF feasibility, and country as independent possible risk factors.

RESULTS

PATIENTS. The 301 patients enrolled in ROUTE (Figure 1) had a mean age of 81.7 ± 5.9 years, with 53.8% being female (Table 1). The mean left ventricular ejection fraction was 52.5 ± 12.2%, a total of 34.9% reported syncope or dizziness on exertion, and 14.2% had angina pectoris class III or IV (Canadian Cardiovascular Society). A high proportion of patients (61.1%) had coronary artery disease, 15.4% had experienced a prior myocardial infarction, 31.4% experienced atrial fibrillation, and 7.6% have previously had a pacemaker implanted. Arterial hypertension was present in 77.3%, peripheral artery disease in 42.5%, pulmonary hypertension in 32.0%, and renal insufficiency in 31.6%. The mean Logistic EuroScore II was 8.8 ± 9.6%; Society of Thoracic Surgeons score was 9.0 ± 7.6%.

TABLE 1 Patient Characteristics

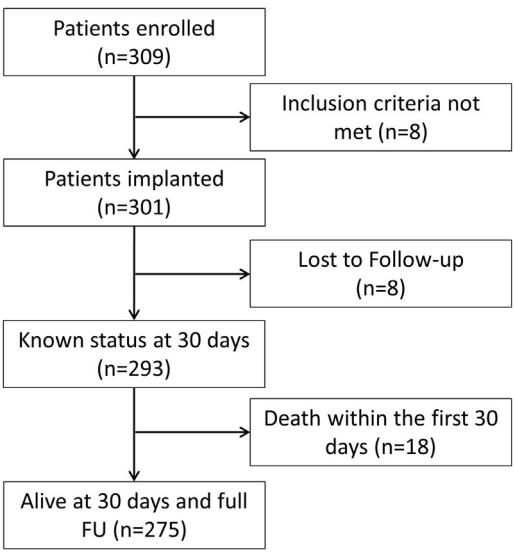
Age, yrs	81.7 ± 5.9
Female	162/301 (53.8)
Current smoker	29/252 (9.6)
Left ventricular ejection fraction, %	52.5 ± 12.2
Syncope/dizziness with exertion	105/301 (34.9)
Angina pectoris CCS class III or IV	40/281 (14.2)
Cardiac comorbidity	
Coronary artery disease	184/301 (61.1)
Prior MI	46/299 (15.4)
Atrial fibrillation	94/299 (31.4)
Prior pacemaker implantation	23/301 (7.6)
Noncardiac comorbidity	
Hypertension	231/299 (77.3)
Diabetes mellitus	79/299 (26.4)
Peripheral artery disease	128/301 (42.5)
Pulmonary disease	78/301 (25.9)
Pulmonary hypertension	95/297 (32.0)
Renal insufficiency or failure	95/301 (31.6)
Surgical risk	
Logistic EuroScore II, %	8.8 ± 9.6
STS score, %	9.0 ± 7.6

Values are mean ± SD or n/N (%).
CCS = Canadian Cardiovascular Society; MI = myocardial infarction; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons.

TAVR ACCESS. In 25.6% of patients, the TAo was the only option due to contraindications for both, the TA and TF approach, whereas 74.4% of patients were deemed feasible to either the TA and/or TF access (72.8% and 13.0%, respectively). In 48.0% of patients (144 of 301), the TAo route was chosen because of a center's preference (Table 2), although TA and/or TF access would have been feasible as well (140 of 144; 97.2%). In 41% of patients, peripheral artery disease or unsuitable vessels were the reasons for using a TAo approach. The TAo access via ministernotomy was chosen in the majority of cases (96.0%).

PROCEDURAL CHARACTERISTICS. The mean duration of the TAVR procedure was 107.0 ± 37.7 min, with the mean fluoroscopy time being 12.4 ± 8.5 min (Table 3). The mean volume of contrast agent used was 101.4 ± 48.6 ml. Balloon aortic valvuloplasty before implantation was used in 74.0% of patients, with a post-dilation rate of 23.3%. Of the 301 performed procedures, the SAPIEN XT valve was implanted in 58.1% of cases and the SAPIEN 3 in 41.9%. Three different valve sizes were used for the TAVR procedures; the 23-mm diameter valve was implanted in 27.7% of patients, the 26-mm diameter in 48.3%, and the 29-mm diameter in 24.0%.

FIGURE 1 Patient Flow



FU = follow-up.

TABLE 2 Access Routes

Reasons for choosing transaortic route	
Standard procedure at site	144/301 (48.0)
Peripheral artery disease	66/301 (22.0)
Vessel status	57/301 (19.0)
Significant respiratory disease	14/301 (4.7)
Poor left ventricular function	8/301 (2.7)
Multiple redo surgery	4/301 (1.3)
High risk for stroke	5/301 (1.7)
Chest wall deformity	2/301 (0.7)
Transaortic access	
Ministernotomy	288/300 (96.0)
Right anterior thoracotomy	12/300 (4.0)
Alternative access routes	
TA feasible	219/301 (72.8)
TF feasible	39/301 (13.0)
Neither TA nor TF feasible	77/301 (25.6)

Values are n/N (%).
TA = transapical; TF = transfemoral; other abbreviations as in Table 1.

PROCEDURAL OUTCOMES. Procedural success was defined as deployment of the Edwards SAPIEN valve without need for a second valve or conversion to conventional surgery, and with no intraprocedural death (Table 4). A second valve was used in 1.7% of patients and conversion to surgery was required in 1.7%. There were no cases of periprocedural death. In 99.0% of patients (297 of 300), the valve was delivered successfully and the catheter was retrieved (no information was available in 3 patients).

The reason for conversion to conventional surgery was valve migration, and left main coronary artery occlusion intraprocedural with need for coronary artery bypass grafting in 1 patient each. In 3 patients, conversion to open surgery was necessary due to access complications (rupture and/or dissection). In total, 2.0% of patients (6 of 300) experienced access complication. Among the patients studied, 0.7% (2 of 300) experienced aortic dissection, 0.7% (2 of 300) aortic rupture, and 1.0% (3 of 300) major bleeding. Patients with major bleedings due to access complications had a surgical intervention without conversion to conventional surgery. Moderate to severe paravalvular regurgitation was detected in 3.3% of patients with the need for reoperation in conventional surgery at day 9 after the procedure in 1 patient. Overall, 19.0% of patients were classified having mild paravalvular leakage.

TABLE 3 Procedural Characteristics

Total procedure time, min	107.0 ± 37.7
Fluoroscopy time, min	12.4 ± 8.5
Quantity of contrast agent used, ml	101.4 ± 48.6
Balloon aortic valvuloplasty	222/300 (74.0)
Balloon post-dilation	70/300 (23.3)
Valve implanted	
SAPIEN XT	175/301 (58.1)
SAPIEN 3	126/301 (41.9)
Valve size implanted, mm	
23	83/300 (27.7)
26	145/300 (48.3)
29	72/300 (24.0)

Values are mean ± SD or n/N (%).

TABLE 4 Procedural Outcomes

Procedural success*	
Second valve used	5/300 (1.7)
Conversion to surgery	5/300 (1.7)
Periprocedural death	0/300 (0.0)
Valve delivered and catheter retrieved‡	297/300 (99.0)
Access complications	6/300 (2.0)
Dissection	2/300 (0.7)
Rupture	2/300 (0.7)
Uncontrolled bleeding	3/300 (1.0)
Procedure aborted	0/300 (0.0)
Paravalvular regurgitation	
Mild	57/300 (19.0)
Moderate	8/300 (2.7)
Severe	2/300 (0.7)
Central regurgitation	
Mild	14/300 (4.7)
Moderate	0/300 (0.0)
Severe	0/300 (0.0)
Intensive care unit stay, days	2.8 ± 5.6
Hospital stay, days	9.9 ± 8.5

Values are n/N (%) or mean ± SD. *Procedural success defined as deployment of one Edwards SAPIEN valve without need for a second valve, no conversion to conventional surgery, and no intraprocedural death. ‡For 3 patients, we were unable to obtain information on valve delivery and catheter retrieval, making 98.7% the worst case.

The aortic valve peak gradient of 71.4 ± 23.2 mm Hg (mean) recorded before the TAVR decreased to 17.6 ± 7.8 mm Hg (mean) after the procedure (Table 5). Similarly, the aortic valve mean gradient decreased from 44.3 ± 15.3 mm Hg (mean) before the procedure to 9.8 ± 4.6 mm Hg (mean) after the procedure ($p < 0.001$ for both, including centers as random factors in the model). Before the intervention, 75.9% of patients were classified as having New York Heart Association functional class III or IV disease, which decreased to 12.1% after the intervention.

FOLLOW-UP OUTCOMES AT 30 DAYS. Overall 30-day mortality was 6.1% (18 of 293), of which 3.1% (9 of 293) was procedure-related mortality and 4.4% (13 of 293) cardiovascular mortality. Other

TABLE 5 Change in Disease-Related Variables

	Pre-Procedure	Post-Procedure
Aortic valve peak gradient, mm Hg	71.4 ± 23.2	17.6 ± 7.8
Aortic valve mean gradient, mm Hg	44.3 ± 15.3	9.8 ± 4.6
	Pre-Procedure	**30 Days**
NYHA functional class I/II, %	72/299 (24.1)	248/282 (87.9)
NYHA functional class III/IV, %	227/299 (75.9)	34/282 (12.1)

Values are mean ± SD or n/N (%).
NYHA = New York Heart Association (33); other abbreviation as in Table 1.

complications included myocardial infarction (1.0%), stroke (1.0%), transient ischemic attack (0.3%), major vascular complications (3.4%), life-threatening bleeding (3.4%), and acute kidney injury (9.5%). A total of 8.8% of patients required permanent pacemaker implantation during the follow-up period. Rehospitalization for valve-related symptoms or deterioration occurred in 3.4% of patients (Table 6).

No influence of age, left ventricular ejection fraction, presence of syncope or dizziness, prior pacemaker implantation, hypertension, peripheral artery disease, pulmonary hypertension, TF feasibility, or country on overall 30-day, procedure-related, or cardiovascular mortality was found in a logistic regression.

DISCUSSION

The results of ROUTE, with 301 patients undergoing TAo-TAVR enrolled, demonstrate that the use of TAo for the implantation of the SAPIEN XT and SAPIEN 3 transcatheter heart valve is a viable alternative approach.

TABLE 6 The 30-Day Outcomes According to VARC-2 Criteria (17)

Overall 30-day mortality	18/293 (6.1)
TAVI-related mortality	9/293 (3.1)
Complication rates	
Cardiovascular mortality	13/293 (4.4)
MI	3/293 (1.0)
Stroke/TIA	4/293 (1.4)
Permanent pacemaker implantation	26/294 (8.8)
Major vascular complication	10/293 (3.4)
Life threatening bleeding	10/293 (3.4)
Acute kidney injury (stage 2 or 3)*	27/285 (9.5)
Hospitalization for valve-related symptoms or deterioration	10/293 (3.4)

Values are n/N (%). *Acute kidney injury post-procedural according to the Acute Kidney Injury Network criteria (17,36).
TIA = transient ischemic attack; VARC = Valve Academic Research Consortium; other abbreviation as in Table 1.

PROCEDURAL CHARACTERISTICS. The patients enrolled in ROUTE had a high mean age with multiple comorbidities, in particular, hypertension, coronary artery disease, and peripheral artery disease. The transaortic route was selected for a number of different reasons. In approximately one-half of cases this was because it was the standard procedure at that particular site. Peripheral vascular disease or unsuitable vessel were other significant reasons for this choice. Such a condition makes the TF route, which is traditionally the preferred option, difficult in many patients (2,6). On the other hand, respiratory disease and poor left ventricular function can be contraindications for the use of TA access (4,7,18,19), conditions that were found in a small proportion of the patients included in the registry.

In contrast to other studies, patients who were suitable for TA- and/or TF-TAVR were not excluded from this registry. In approximately 25% of patients, the TAo was deemed to be the only option, whereas approximately 70% of patients that underwent TAo-TAVR were also suitable for a TA procedure. A preference for the TAo route in these patients may have been due to its less invasive nature, and the decreased risk of left ventricular wall injury or major bleeding complications (15,20). Furthermore, surgeons are generally more familiar with aortic perforation in comparison with piercing the apex of the heart, because aortic perforation is common in open cardiac procedures (12). This is likely to be a contributing factor to the reported steep learning curve associated with TA-TAVR (15,21–23).

PERIPROCEDURAL OUTCOMES. The mean procedure time was similar to or lower than those previously reported for TAo-TAVR, and similar proportions of the different sizes of SAPIEN valves were used (6,24). Procedural success was high, with only small percentages of patients requiring a second valve (1.7%) or conversion to open surgery (1.7%). The rates of these procedural complications were lower than those reported for TAo-TAVR by Amrane et al. (9) in 44 patients using different valve types (6.8% and 4.6%, respectively), whereas Hayashida et al. (6), evaluating the efficacy and safety of the TAo-TAVR approach using either the SAPIEN XT or CoreValve (Medtronic, Minneapolis, Minnesota), reported conversion to open surgery in 5.3% of cases. Thourani et al. (24) reported a rate of open heart surgery conversion of 2.8%. However, in another study, no second valves were required and no patients

underwent conversion to conventional surgery (15). The values noted in the present registry are generally comparable to those previously reported for TF-TAVR (1.1% to 2.4% for a second valve; 0.8% to 1.7% for conversion to conventional surgery) (14,25–28), and for the TA route (0.7% to 2.8% for a second valve; 1.0% to 3.9% for conversion to conventional surgery) (14,21,24,26–28). No deaths occurred during the TAo-TAVR procedures included in the present registry, which is in agreement with the low numbers reported in other studies (6,9,15,24).

There were very few access complications found when using the TAo-TAVR procedure. This is likely due to the familiarity of surgeons with aortic interventions. In comparison, ventricular damage and bleeding have been previously associated with the TA access route (14,15,20,29). Furthermore, the occurrence of arterial injury when using the TF route is notable (14,30,31).

In general, paravalvular and central regurgitation were of a mild nature, with only 2 cases of severe paravalvular leakage documented. In comparison, moderate or severe paravalvular regurgitation have been reported in 11% of patients with TAo access versus 12% by using the TA approach (15).

POST-PROCEDURAL OUTCOMES. A significant decrease in aortic valve peak gradient was noted post-procedural, with a similar drop found for the mean gradient ($p < 0.001$ for both). Comparable reductions in pressure gradients have been reported by Thourani et al. (7,32) for TAo-, TA-, and TF-TAVR using the SAPIEN valve. The extent of heart failure symptoms, as categorized according to the New York Heart Association functional class criteria (33), was also greatly decreased by the TAVR. The proportion of patients who were asymptomatic or had mild symptoms increased significantly. Accordingly, the percentage that had severe limitations in activity because of their symptoms decreased to below 15%.

At 30 days after the procedure, overall mortality was assessed to be 6.1%, a value that is similar to that reported by Hayashida et al. (6) (7.4%) and Amrane et al. (6.8%) (9), but significantly lower than that documented by Lardizabal et al. (15) (14.0%) and Thourani et al. (24) (10.3%). In comparison, studies regarding TA-TAVR have demonstrated overall 30-day mortalities of 8.8% to 18.2% (14,15,24,26,27), whereas published values associated with use of TF access are 8.0% to 11.1% (14,26,31,32). In the present registry, cardiovascular mortality at 30 days was found to be 4.4%, with TAVR-related mortality being 3.1%. Lardizabal et al. (15) reported cardiovascular mortality of 2.0% for TAo-TAVR, whereas the value documented for TA access was higher at 12.0%.

Other complications reported at the 30-day follow-up were myocardial infarction, stroke or transient ischemic attack, life-threatening bleeding, and acute kidney injury; however, the incidences of these events were low, similar to other studies. Of note, 8.8% of patients required permanent pacemaker implantation within the first 30 days after the TAo-TAVR. This value is similar, albeit slightly lower, compared with that reported by Amrane et al. (9) (11.4%) and that by Tanawuttiwat et al. (29) (12.5%), both for TAo. In contrast, the values previously published for TA-TAVR are much lower at 5.6% to 7.3% (14,29,31). It has been shown previously that implantation of the replacement valve further into the ventricle is associated with a greater chance of left bundle branch block (34,35). It is, therefore, possible that the positioning of the SAPIEN valve using the TA approach may result in a lower incidence of left bundle branch block, and accordingly, less need for permanent pacemaker implantation.

STUDY LIMITATIONS. Although it provides a wealth of information regarding the efficacy and safety of TAo-TAVR, the establishment of this registry has some limitations. First, although the surgeons all underwent extensive training in the use of TAo-TAVR with the SAPIEN valves, the analysis may still be affected by a learning curve. Second, experience with the procedure is likely to vary with site; however, the requirement for a minimum of 5 prior implantations should go some way to reducing any bias associated with this. Finally, the follow-up period was confined to 30 days, meaning that complications in the longer term were not recorded. A longer follow-up time would provide more extensive information regarding the safety and efficacy of the TAo-TAVR procedure. Therefore, we are currently collecting data for the 1-year follow-up in these patients.

CONCLUSIONS

ROUTE demonstrates that the use of TAo for the implantation of the SAPIEN XT and SAPIEN 3 transcatheter heart valves is a viable alternative to TA procedures. The high success rate and low occurrence of complications, both during the procedure and in the subsequent 30 days, reveal the excellent efficacy and safety of the technique. Furthermore, overall 30-day mortality was found to be low.

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PERSPECTIVES

WHAT IS KNOWN? Transapical and transfemoral transcatheter aortic valve replacement (TAVR) is a safe alternative to surgery in high risk patients.

WHAT IS NEW? Transaortic TAVR is a newly developed technique for patients ineligible for transapical and transfemoral TAVR, but reported experience so far relies on single center reports. We conducted a multicenter, multinational prospective registry for transaortic TAVR showing that it is a safe and effective option with favorable outcomes.

WHAT IS NEXT? The results call for a direct comparison of the 2 surgical access routes TAo and transaortic TAVR.

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