Safety and Efficacy of the Subclavian Approach for Transcatheter Aortic Valve Implantation With the CoreValve Revalving System

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Background—Transcatheter aortic valve implantation (TAVI) is a new option for patients with severe aortic stenosis at high surgical risk. The standard retrograde approach through the femoral artery is contraindicated in case of unfavorable iliofemoral anatomy or extensive disease. In these patients, a trans-subclavian approach may be feasible.

Methods and Results—Between June 2007 and July 2009, TAVI with the CoreValve bioprosthesis (Medtronic, Minneapolis, Minn) was performed in 514 consecutive patients at 13 Italian hospitals, using the subclavian approach in 54 cases. The median logistic EuroSCORE was significantly higher in the subclavian (19.4; interquartile range, 12.5 to 29.8) versus femoral group (25.3; interquartile range, 15.1 to 36.6) \((P=0.03)\), as well as the rate of comorbidities. Procedural success was obtained in 100% versus 98.4% of the subclavian versus femoral groups, respectively \((P=0.62)\), with intraprocedural mortality of 0% versus 0.9% \((P=1.00)\). The most common in-hospital complications were a new left bundle-branch block (22.4%) and the need for pacemaker (16.3%). No specific complications for the subclavian access (vessel rupture, vertebral or internal mammary ischemia) were reported. The learning curve for the subclavian approach led to a wider use of local anesthesia. Thirty-day mortality was 0% versus 6.1% in the subclavian versus femoral groups, respectively \((P=0.13)\). Six-month mortality rate was 9.4% versus 15.8% \((P=0.44)\), whereas valve-related adverse events were 13.6% versus 13.9% \((P=0.79)\).

Conclusions—TAVI through the subclavian approach appeared feasible and safe, with excellent procedural success and low in-hospital complication rates. This new technique allows patients with contraindications to the femoral approach to be treated with TAVI. (Circ Cardiovasc Interv. 2010;3:359-366.)

Key Words: aortic valve ■ aortic stenosis ■ transcatheter aortic valve implantation

Severe degenerative aortic stenosis (AS) is typical of elderly patients with multiple comorbidities that increase surgical risk and jeopardize prognosis. In such patients, transcatheter aortic valve implantation (TAVI) for the treatment of critical AS has demonstrated encouraging results, showing that this new treatment can be safe and effective in inoperable patients and in patients at high risk for surgery.1–4

Clinical Perspective on p 366

The less invasive approach for both types of valves developed for TAVI currently available is through the common femoral artery. Both the Edwards SAPIEN (Edwards Lifesciences LLC, Irvine, Calif) and the CoreValve Revalving System (CoreValve Inc, Irvine, Calif; currently Medtronic, Minneapolis, Minn) can be delivered in most of the screened patients using the transfemoral approach, usually with a fully percutaneous technique for the CoreValve, which requires an 18F sheath. The femoral approach is contraindicated in patients with excessive atherosclerosis, calcifications, or tortuosity of common femoral arteries or iliac arteries and should be considered cautiously in patients with an aneurysm of the thoracic or abdominal aorta. To treat these patients, a transapical approach has been described as an alternative option with good results for the Edwards SAPIEN prosthesis.5–7 The transapical approach avoids the problems of vascular access but adds adjunctive risks to TAVI, because
of general anesthesia, thoracotomy, and incision of the apex of the left ventricle, which can be structurally friable in elderly patients and in case of severe hypertrophy. Moreover, the transapical approach requires a dedicated antegrade delivery system.

Very recently, a few cases of CoreValve implantation through the subclavian/axillary artery with the standard retrograde delivery system have been described in patients with contraindications to the femoral approach.8–11

In the present multicenter, prospective cohort study, we report the procedural and short-term results of the initial experience of CoreValve implantation through the subclavian approach from 2008 to August 2009 in Italy.

Methods

Since the first CoreValve implantation in Italy in June 2007, a Web-based prospective registry was made available to all centers performing TAVI with this device. This registry includes baseline clinical, laboratory, echocardiographic, computed tomography (CT), and angiographic data, as well as procedural data and follow-up data at 1, 3, 6, 12, and 24 months. We analyzed the baseline, procedural, and follow-up data of all patients, comparing the subclavian and femoral approaches. The study was approved by the institutional review committees, and written informed consent was obtained from the patients.

Patient Selection

All patients with severe symptomatic AS (calculated aortic valve area ≤1 cm²) referred for possible TAVI because of high surgical risk were evaluated at each center by a multidisciplinary team consisting of interventional and clinical cardiologists, cardiac surgeons, and cardiac anesthesiologists. Eligibility for TAVI included either compassionate use or meeting the criteria described by Grube et al,4 which were used for the initiation of the CoreValve implantation program in Italy.

Starting from January 2008, patients eligible for TAVI with the CoreValve system who had contraindications to the femoral approach were considered for the left subclavian approach. In these patients, the diameter, tortuosity, and calcium distribution of the left axillary and subclavian arteries were analyzed by means of angiography and CT scan, with particular attention to the origin of the subclavian artery from the aortic arch. Patients were not eligible for the subclavian approach in case of vessel diameter <6 mm, heavy calcifications, excessive tortuosity, or tight subclavian stenosis not amenable to percutaneous balloon angioplasty. The presence of a patent left internal mammary artery graft to a coronary artery was not amenable to percutaneous balloon angioplasty. The presence of a patent left internal mammary artery graft to a coronary artery was not considered a contraindication to the subclavian approach, provided that the subclavian artery was larger than 7 mm and free from atherosclerotic disease.

Technique of TAVI With the Subclavian Approach

The current third-generation CoreValve Revalving system was used in all patients. The CoreValve aortic valve prosthesis consists of a trileaflet bioprosthetic porcine pericardial tissue valve, which is mounted and sutured inside a self-expanding nitinol frame. Further details have been described previously.12

The left subclavian/axillary artery was usually chosen rather than the right because it allows for a more favorable orientation of the CoreValve delivery system through the aortic annulus, in a fashion quite similar to that of the femoral approach. In all cases, the subclavian/axillary artery was isolated and prepared for sheath insertion by a cardiac or vascular surgeon, using standard surgical technique. The artery was punctured with Seldinger technique in the middle of a purse-string suture, and a 6F sheath was inserted to advance a diagnostic catheter inside the left ventricular cavity. Subsequently, the same 18F sheath used for the femoral approach was advanced over a stiff guide wire through the subclavian artery into the aortic arch and ascending aorta, just below the origin of the brachiocephalic artery. From this point onward, TAVI through the subclavian/axillary approach was performed with the same technique used for the femoral approach. At the beginning of our experience, general anesthesia was used in all patients both for femoral and subclavian approaches. After the first few cases, however, local anesthesia in combination with mild systemic sedative/analogic treatment was used whenever possible. Balloon valvuloplasty with a 22- or 25-mm balloon was performed under rapid pacing (160 to 180 bpm) before CoreValve deployment. Aspirin (100 mg/d) was administered before the procedure and continued indefinitely. In addition, all patients received ciprofloxacin (300-mg loading dose), followed by 75 mg daily for 3 to 6 months. During the intervention, the patient received weight-adjusted intravenous heparin to achieve an activated clotting time of 200 to 250 seconds for the duration of the procedure.

Definitions and Follow-Up

Procedural success was defined as implantation of a functioning prosthetic valve within the aortic annulus, with stable hemodynamic conditions, absence of severe paravalvular regurgitation, and without intraprocedural mortality. Suboptimal positioning of the CoreValve, with the ventricular margin of the nitinol frame either too deep in the outflow tract, or too high at the level of the aortic annulus, was not considered a procedural failure, unless it caused severe regurgitation that was still present at the end of the procedure. Procedure-related events were defined as occurring during or as a direct result of the procedure. Renal failure was defined according to RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) criteria.13 Major vascular injury was defined as vascular rupture with fatal bleeding or need for urgent vascular surgery or dissection of the aorta.14 Major adverse cardiac and cerebrovascular events (MACCEs) included death, myocardial infarction, stroke, or reintervention on the aortic valve. Major adverse valve-related events (MAVREs) included valve-related mortality, valve-related morbidity, and need for new permanent pacemaker or defibrillator within 14 days after the procedure.14 Valve-related morbidity was defined as any structural deterioration or nonstructural prosthesis dysfunction, valve thrombosis, embolism, bleeding events, and prosthetic valve endocarditis. Frailty was defined according to the criteria of Fried et al.15 Clinical follow-up through office visits was carried out at 1 and 6 months and every 6 months afterward. The occurrence of MACCEs and MAVREs was evaluated at each follow-up. Patients in whom valve implantation was unsuccessful were followed up for 30 days after the procedure.

Statistical Analysis

Categorical variables were expressed as a number and percentage of patients. Continuous parameters were expressed as medians and interquartile range. Differences between treatment groups were assessed by Fisher exact or χ² test for categorical variables and by Student t test or Wilcoxon rank-sum test, as appropriate. In the subanalysis comparing procedural results between the first 4 subclavian cases and the subsequent cases performed in the 5 most experienced centers, we used a GEE model to better control for differences by center. Actuarial freedom from adverse events was assessed with Kaplan–Meier method, and differences between groups were evaluated with the exact log-rank test. Statistical tests were performed with STATA 10 (StataCorp LP, College Station, Tex) and StatXact 9 (Cytel Inc, Cambridge, Mass) software. A 2-tailed value of P<0.05 was considered statistically significant.

The authors had full access to and take responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Population

Between June 2007 and July 2009, a total of 514 consecutive patients who underwent CoreValve implantation at 13 cath-
eterization laboratories in Italy were enrolled in a prospective registry. Of these patients, 54 were treated using the subclavian approach in 10 of 13 centers, with a mean of 5.4 patients per laboratory (range, 1 to 12). Baseline characteristics of the patients, grouped according to the vascular access, are reported in Table 1. The high surgical risk of our patients is documented by the median logistic EuroSCORE of 20.1 (interquartile range, 12.8 to 30.5), with the subclavian group showing a significantly higher EuroSCORE ($P = 0.03$). Patients treated by the subclavian access were less frequently in New York Heart Association class III or IV, but they had significantly higher rates of comorbidities including peripheral artery disease, coronary artery disease, carotid artery stenosis, prior myocardial infarction, and prior percutaneous coronary intervention. The subclavian group also showed a trend to a higher rate of prior cerebrovascular accidents and of severe chronic obstructive pulmonary disease.

### Procedural Results

The main procedural results and in-hospital complications are summarized in Table 2. Procedural success was obtained in 98.4% and 100% of the femoral and subclavian groups, respectively ($P = 0.62$). The reasons for 7 unsuccessful procedures in the femoral group were conversion to open heart surgery in 5 patients (1.1%) and no CoreValve deployment because of a too-large aortic annulus (underestimated at CT scan and echocardiography) in 2 patients (0.4%). A suboptimal positioning (either too low or too high) of the CoreValve was not infrequent (13.8%), being more common with the femoral approach (5.6 versus 14.8%; $P = 0.06$). However, the implantation of a second CoreValve prosthesis inside of the first one because of severe paravalvular regurgitation was required only in 4.3% of the femoral cases and in no subclavian case. The surgical access to the subclavian artery significantly prolonged procedural duration ($P = 0.0001$) but not fluoroscopy time.

Postprocedural peak and mean transaortic gradients were markedly low in both groups (Table 2). A mild paravalvular leak was observed in 59.9% and 73.0% of the femoral and subclavian groups, respectively ($P = 0.16$), whereas it was moderate in 20.8% and 13.5%, respectively ($P = 0.30$). Intra-procedural mortality rate was 0.9% in the femoral group and 0% in the subclavian group ($P = 1.00$). The most common in-hospital complications were the onset of a left bundle-
branch block (22.4%) and the need for pacemaker (16.3%). Severe bleeding requiring transfusion of ≥5 U of packed red blood cells was infrequent (3.1%), as was acute renal failure (2.9%), stroke (1.8%), major vascular surgery (1.8%), cardiac tamponade (1.4%), and septicemia (0.4%). No significant differences between the femoral and subclavian approaches were observed. Perioperative stroke was not related to the vertebrobasilar circulation in the single patient of the subclavian group who had cerebral ischemia. In addition, the subclavian approach never caused brachial plexus injuries. To evaluate the potential impact of the specific learning curve for the subclavian approach, we compared the procedural results of the first 4 subclavian cases versus the subsequent cases in the 5 centers who performed at least 5 subclavian access procedures (Table 3). The only significant difference was a marked decrease in the use of general anesthesia, from 80.0%

Table 3. Comparison of Procedural Results and In-Hospital Complications of the First 4 Subclavian Cases Versus the Subsequent Cases Performed in the 5 Centers That Performed at Least 5 Subclavian Access Procedures

<table>
<thead>
<tr>
<th></th>
<th>First 4 Subclavian Cases per Center (n=20)</th>
<th>Subsequent Subclavian Cases (n=15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>General anesthesia, n (%)</td>
<td>16 (80.0)</td>
<td>6 (40.0)</td>
<td>0.02*</td>
</tr>
<tr>
<td>High or low implantation, n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>New left bundle-branch block, n (%)</td>
<td>6 (30.0)</td>
<td>4 (26.7)</td>
<td>0.68</td>
</tr>
<tr>
<td>New pacemaker, n (%)</td>
<td>6 (30.0)</td>
<td>3 (20.0)</td>
<td>0.76</td>
</tr>
<tr>
<td>Fluoroscopy time, min (range)</td>
<td>25 (15–33)</td>
<td>20 (18–35)</td>
<td>0.57</td>
</tr>
<tr>
<td>Procedure duration, min (range)</td>
<td>110 (79–127)</td>
<td>120 (86–127)</td>
<td>0.44</td>
</tr>
<tr>
<td>Transfusion ≥3 packed cells units, n (%)</td>
<td>1 (5.0)</td>
<td>1 (6.7)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

*Significant difference between groups.
to 40.0% (P=0.02), whereas procedural duration and complications did not differ.

### Clinical Outcome

The median follow-up of the 514 patients was 6.9 months (interquartile range, 2.8 to 11.4 months), being slightly longer for the femoral versus subclavian group (7.8±6.2 versus 6.2±4.5 months; P=0.07). The rates of adverse events at 30 days and 6 months are detailed in Table 4. Overall 30-day mortality was 5.4%, being 6.1% in the femoral group and 0% in the subclavian group (P=0.13). Mortality remained relatively low and similar in both groups at 6-month follow-up.

### Discussion

Degenerative aortic stenosis is a growing problem with ageing of the population in western countries; moreover, many elderly patients are at higher risk for traditional surgical intervention and frequently they are not referred for surgery, even though the prognosis of untreated symptomatic aortic stenosis is poor.16–18 Since the first report by Cribier of...
percutaneous implantation of a balloon-expandable aortic valve in 2002, followed by the introduction of the self-expanding CoreValve device in 2004. TAVI has been proposed as a new alternative procedure for elderly patients with aortic degenerative valve disease, and currently thousands of patients have been successfully implanted in different countries. Different types of approaches have been suggested: from the first antegrade-transeptal approach to the more common retrograde femoral approach, to the transapical access. Recently, a position statement of the European Society of Cardiology has accepted this procedure as feasible and safe, both with the retrograde approach and with the transapical one. The latter is especially used with the SAPIEN balloon-expandable device in patients presenting with iliofemoral severe calcifications, tortuosity, small diameter, or severe atherosclerotic disease of the aorta.

As a new alternative to both the femoral and transapical access, the subclavian/axillary approach has been recently proposed for the CoreValve system, and a very few cases have been described.

**Procedural Results**

The present study reports the initial experience of CoreValve implantation through the subclavian/axillary approach in 54 consecutive patients from the Italian CoreValve registry. Procedural success was obtained in 100% of the patients, with no periprocedural death. Such excellent result may depend on the fact that the subclavian approach was performed by physicians who already had achieved a good level of proficiency with CoreValve implantation through the femoral access. This is confirmed by the similar rates of procedural success and duration between the first 4 subclavian cases and those performed afterward in the centers with the largest subclavian experience. In addition, although the anatomic location of the subclavian artery is unfavorable in case of vessel rupture, we did not observe any access site complication in this series of patients. The extremely careful surgical technique used for vessel preparation and the direct visual control of the access site underlie this important result. Interestingly, the sharp 90° bend that the left subclavian artery makes shortly after its origin from the aortic arch did not represent a problem for the advancement of the 18F sheath toward the ascending aorta. On the contrary, the very short distance between the vascular access and the aortic valve allowed for better control of the CoreValve system during prosthesis deployment, with a lower rate of deep prosthesis implantation in the left ventricular outflow tract, compared with the femoral approach. In fact, the implantation of a second CoreValve prosthesis because of severe paravalvular regurgitation due to low implantation of the first prosthesis was never required with the subclavian access. Actually, the subclavian approach allows for a better alignment between the CoreValve delivery catheter and the axis of the aortic root. As a low prosthesis implantation has been suggested as the possible mechanism for postprocedural high-degree atrioventricular block, we could expect that a better control of prosthesis deployment from the subclavian approach would translate into a lower rate of new permanent pacemaker implantation. However, this was not observed, and we think that in our subclavian population the need for new pacemaker implantation was related to factors other than the level of prosthesis implantation because the rate of suboptimal implantation was very low for the subclavian access (5.6%).

An important caveat when dealing with the left subclavian artery is represented by the risk of impairing flow in the left internal mammary artery, when the latter has been used as a graft to a coronary artery in a previous intervention. In our series of 54 patients treated through the subclavian approach, 8 had a patent left internal mammary artery graft. To reduce the duration of the interference of the 18F sheath with this branch, we withdrew the 18F introducer before the origin of the left internal mammary artery immediately after the advancement of the CoreValve prosthesis across the aortic annulus, thus preventing flow impairment in the mammary artery during CoreValve deployment. With this technique, we did not observe any fall in arterial pressure or signs of myocardial ischemia at the ECG during the procedure.

**Clinical Outcome**

Overall survival as well as freedom from MACCEs and MAVREs at 1 and 6 months were similar between patients treated through the subclavian approach and patients treated through the femoral approach, with a very high 6-month survival in both groups (88.6% versus 93.3%, femoral versus subclavian, respectively). This result is particularly relevant considering that patients treated through the subclavian approach had significantly more comorbidities compared with patients undergoing transfemoral CoreValve implantation, as shown by the significantly higher EuroScore. In fact, on top of the obviously higher rate of peripheral artery disease, the subclavian population showed significantly higher rates of coronary artery disease, carotid artery stenosis, prior myocardial infarction, prior percutaneous coronary intervention, and a trend to a higher rate of prior cerebrovascular accidents and of severe chronic obstructive pulmonary disease.

**Comparison With the Transapical Approach**

The clinical profile of the patients treated with the subclavian approach in our experience looks similar to that of patients treated by the transapical approach with the Edwards SAPIEN valve, as indicated by the mean logistic EuroSCORE of 27% and 37% reported by Walther and Ye, respectively. The transapical approach has been demonstrated to be a valid alternative to the femoral access, as acknowledged by the recent position statement of the European Society of Cardiology. However, this approach has specific contraindications, including previous left ventricular patch surgery, calcified pericardium, severe respiratory insufficiency, and nonreacheable left ventricular apex. In addition, the transapical approach requires a hybrid operating room and appears more time-consuming, with an average procedural duration of 148±92 minutes, which compares unfavorably with the 106±29 minutes of the subclavian approach in our registry. Moreover, although the transapical approach can be performed with minimally invasive surgical technique, it usually requires general anesthesia and sometimes cardiopulmonary bypass. On the contrary, the subclavian approach can be performed under simple local anesthesia in many cases after...
the initial learning curve. Although no direct comparison between the two approaches has even been performed, the need for general anesthesia, thoracotomy, and ventriculotomy with the transapical approach probably requires a longer postoperative recovery. With respect to procedural and clinical results, the reports on the transapical approach describe a procedural success rate of 94% to 96%, with a conversion to open chest surgery of 0% to 6%, and a 30-day mortality rate of 8% to 23%.

Limitations
This registry has limitations common to all nonrandomized studies, including the limited number of patients in the subclavian group. However, we verified through the Italian distributor of CoreValve that all patients who underwent TAVI with the subclavian approach in Italy were actually entered in the registry, and none of them was lost at follow-up. In addition, this is the largest experience of subclavian approach for CoreValve implantation ever reported.

Conclusion
The results of TAVI with the CoreValve ReValving System through the subclavian approach in this multicenter registry showed that this approach is feasible and safe, with excellent procedural success and low in-hospital complication rates, similar to those of the standard femoral approach. This new technique did not require a relevant learning curve, as procedural and short-term clinical results were highly satisfactory even in the initial cases. Therefore, vascular access through the subclavian artery can be considered a valid strategy in patients with contraindications to the femoral approach, allowing for enlargement of the eligibility for TAVI with the CoreValve.

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Disclosures
None.

References
CLINICAL PERSPECTIVE

Whether the subclavian artery can be used as the vascular approach for transcatheter aortic valve implantation (TAVI) is a particularly significant question because a number of patients screened for TAVI have contraindications for femoral access. Our report describes the procedural results of TAVI with the CoreValve Revalving System placed through the subclavian artery in 54 consecutive patients. Procedural success was obtained in 100% of the subclavian access patients, with no intraprocedural deaths. The most common in-hospital complications were a new left bundle-branch block (27.8%) and the need for pacemaker (18.5%). No specific complications related to subclavian access (vessel rupture, vertebral or internal mammary ischemia) were observed. Six-month mortality was 9.4%, whereas the rate of valve-related adverse events was 13.6%. When comparing the outcomes of these patients with those treated by the femoral artery approach, no significant differences were observed. Our preliminary data show that the subclavian approach is safe and feasible, with excellent procedural success and low in-hospital complication rates, similar to those of the femoral approach. Interestingly, the subclavian approach did not require a learning curve. Vascular access through the subclavian artery may expand the proportion of patients with aortic stenosis for treatment by TAVI.