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2-Year Results of CoreValve Implantation Through the Subclavian Access

A Propensity-Matched Comparison With the Femoral Access

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Objectives The goal of this study was to assess the procedural and 2-year results of the subclavian approach for transcatheter aortic valve implantation (TAVI) compared with those of the femoral approach by using propensity-matched analysis.

Background The subclavian approach with the CoreValve prosthesis (Medtronic, Inc., Minneapolis, Minnesota) represents an interesting opportunity when the femoral access is unfeasible.

Methods All consecutive patients enrolled in the Italian CoreValve Registry who underwent TAVI with the subclavian approach were included. Propensity score analysis was used to identify a matching group of patients undergoing femoral TAVI.

Results Subclavian approach was used in 141 patients (61% men; median age 83 years; median logistic European System for Cardiac Operative Risk Evaluation score 23.7%). The femoral group of 141 patients was matched for baseline clinical characteristics, except for peripheral artery disease. The 2 groups showed similar procedural success (97.9% vs. 96.5%; $p = 0.47$), major vascular complications (5.0% vs. 7.8%; $p = 0.33$), life-threatening bleeding events (7.8% vs. 5.7%; $p = 0.48$), and combined safety endpoint (19.9% vs. 25.5%; $p = 0.26$). The subclavian group showed lower rates of acute kidney injury/stage 3 (4.3% vs. 9.9%; $p = 0.02$), of minor vascular complications at the 18-F sheath insertion site (2.1% vs. 11.3%; $p = 0.003$), and of all types of bleeding events related to vascular complications. Survival at 2 years was 74.0 ± 4.0% in the subclavian group compared with 73.7 ± 3.9% in the femoral group ($p = 0.78$). The 2-year freedom from cardiovascular death was 87.2 ± 3.1% versus 88.7 ± 2.8% in the subclavian versus femoral group, respectively ($p = 0.84$).

Conclusions The subclavian approach for TAVI is safe and feasible, with procedural and medium-term results similar to the femoral approach. Subclavian access should be considered a valid option not only when the femoral approach is impossible but also when it is difficult, albeit feasible. (J Am Coll Cardiol 2012;60:502–7) © 2012 by the American College of Cardiology Foundation

About one-third of candidates for transcatheter aortic valve implantation (TAVI) suffer from severe peripheral artery disease, making the routine femoral approach difficult or impossible. Currently, the alternatives to the femoral approach are the transapical (1), the subclavian (2), and the direct aortic access (3). In the current study, we report the 2-year results of the subclavian approach for TAVI with the CoreValve prosthesis (Medtronic, Inc., Minneapolis, Minnesota) in the largest cohort of consecutive patients described so far compared with a propensity-matched cohort of patients undergoing TAVI through the femoral approach.

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Methods

Patient population. Since June 2007, all consecutive patients undergoing TAVI with the 18-F CoreValve prosthesis at 13 Italian centers were prospectively enrolled in the Italian CoreValve Registry. Patient eligibility criteria, registry design, and technical details of the procedure have been described elsewhere (2,4,5). The study was approved by the institutional ethics committees, and written informed consent was obtained from all patients.

Since January 2008, all patients with small (diameter <6 mm) or severely diseased iliofemoral arteries were evaluated for the feasibility of the subclavian approach by means of angiography, multislice computed tomography, and Duplex ultrasound. Subclavian access was excluded in case of vessel diameter <6 mm, heavy calcifications, excessive tortuosity, and severe stenosis not amenable to balloon angioplasty. Presence of a permanent pacemaker in the left pectoral region was not considered a contraindication, nor was the presence of a patent left internal mammary artery (LIMA) coronary graft, provided that the subclavian artery diameter was >7 mm.

The subclavian TAVI technique and anesthetic management have been described previously (2,6).

Definitions. In October 2011, the information contained in the web-based registry were re-evaluated by the Steering Committee to conform to the definitions proposed by the Valve Academic Research Consortium (7). Device success, all-cause mortality, cardiovascular mortality, myocardial infarction, stroke, vascular complications, bleeding complications, 30-day combined safety endpoint, and 2-year combined efficacy endpoint were re-assessed.

Statistical analysis. Continuous variables are presented as mean ± SD or as median (interquartile range) and were compared using the 2-tailed Student *t* test or the Mann-Whitney *U* test, as appropriate. Categorical variables were compared by using the chi-square test or Fisher exact test, as appropriate. The cumulative incidences of clinical events at follow-up were assessed by using the Kaplan-Meier method, and the log-rank test was used for comparison between groups. A p value <0.05 was considered statistically significant.

To identify a comparable group of patients undergoing femoral TAVI, propensity analysis was performed on 927 femoral patients enrolled in the Italian CoreValve Registry. The propensity score was calculated by using a logistic regression model that included the following variables: age, sex, coronary artery disease, pulmonary hypertension, previous aortic valvuloplasty, previous stroke, left ventricular ejection fraction, and serum creatinine >2.0 mg/dl. Matching was performed by randomly selecting a subclavian patient and looking for the femoral patient with the nearest logit-transformed propensity score.

All data were processed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois).

Results

Abbreviations and Acronyms

LIMA = left internal mammary artery

TAVI = transcatheter aortic valve implantation

Patient population. Between June 2007 and March 2011, a total of 141 of 1,068 consecutive patients enrolled in the Italian CoreValve Registry were treated with the subclavian access in 10 centers, with a median number of 8 cases (range 4 to 36). The overall rate of subclavian access in the registry rose from 9.0% in 2008 to 20.0% in 2011. The propensity score used to identify a matched femoral access cohort showed a good discriminative power (C-statistic 0.70). Baseline demographic characteristics were similar between the 2 groups (Table 1), except for peripheral artery disease, which was more prevalent in the subclavian group ($p < 0.0001$). Twelve patients (8.5%) of the subclavian group had a patent LIMA.

Procedural results. The left subclavian artery was used in 96% of subclavian patients. Device success was similarly high in both groups ($p = 0.47$), with a lower rate of local anesthesia in the subclavian group ($p < 0.0001$) (Table 2). Overall procedural time was longer in the subclavian group because of the surgical vascular access ($p < 0.0001$), whereas fluoroscopy time was similar ($p = 0.15$).

Procedural mortality was very low in both groups ($p = 0.56$). No patient with a patent LIMA undergoing TAVI through the left subclavian artery showed signs of myocardial ischemia during the procedure. In addition, no brachial plexus injuries were observed.

In-hospital outcome. In-hospital events are defined in Table 3. Mortality was entirely due to cardiovascular causes and was similar between groups ($p = 0.78$), as well as stroke, myocardial infarction, new left bundle branch block, and new permanent pacemaker implantation. Conversely, the rate of acute kidney injury/stage 3 was significantly lower in the subclavian group ($p = 0.02$).

Table 1 Demographic Characteristics

Characteristic	Subclavian Access	Femoral Access	p Value
Age (yrs)	83.0 (78.9–87.0)	83.0 (78.6–86.1)	0.25
Female	55 (39.0)	60 (42.3)	0.54
Logistic EuroSCORE	23.7 (15.8–33.6)	23.3 (13.5–32.7)	0.32
Peripheral artery disease	120 (85.1)	29 (20.6)	<0.0001
Coronary artery disease	83 (58.9)	69 (48.9)	0.09
Previous coronary revascularization	68 (48.2)	53 (37.6)	0.07
Previous stroke	18 (12.8)	13 (9.2)	0.34
Serum creatinine >2 mg/dl	19 (13.5)	12 (8.5)	0.24
NYHA functional class III/IV	102 (72.3)	96 (68.0)	0.86
Left ventricular ejection fraction (%)	54 (41–60)	52 (40–60)	0.27
Peak aortic gradient (mm Hg)	82.4 ± 20.8	81.9 ± 21.4	0.83
Mean aortic gradient (mm Hg)	50.2 ± 14.2	50.1 ± 14.1	0.96

Values are median (interquartile range), n (%), or mean ± SD.
EuroSCORE = European System for Cardiac Operative Risk Evaluation score; NYHA = New York Heart Association.

JACC Vol. 60, No. 6, 2012
August 7, 2012:502–7

Table 2 Procedural Results

Outcome	Subclavian Access	Femoral Access	p Value
Device success	138 (97.9)	136 (96.5)	0.47
Procedural mortality	2 (1.4)	1 (0.7)	0.56
Local anesthesia	65 (46.1)	118 (83.7)	<0.0001
Fluoroscopy time (min)	18 (14–27)	21 (15–30)	0.15
Procedural time (min)	120 (89–127)	75 (60–120)	<0.0001
29-mm CoreValve*	80 (56.7)	71 (50.4)	0.28
CoreValve-in-CoreValve	2 (1.4)	6 (4.3)	0.17
CoreValve migration	1 (0.7)	1 (0.7)	0.96
Conversion to surgery	1 (0.7)	1 (0.7)	0.99

Values are n (%) or median (interquartile range). *Medtronic, Inc., Minneapolis, Minnesota.

The rates of major vascular complications (p = 0.33) and minor vascular complications (p = 0.16) were similar between groups. In particular, the major subclavian artery complications were as follows: tear of the vessel wall at the site of sheath insertion in 3 cases, requiring covered stent implantation in 2 cases and prolonged external hemostasis in 1; longitudinal vessel dissection in 3 cases, requiring stent implantation in 2; and acute asymptomatic subclavian thrombosis in 1 case, resolved with local thrombolytic administration. Of note, minor vascular complications in the subclavian group were often related to the simultaneous 6-F femoral access; consequently, minor vascular complications at the site of 18-F sheath insertion were significantly lower in the subclavian group (p = 0.003) (Fig. 1).

All types of bleeding complications were also similar between groups (Table 3). When considering only bleeding events directly related to vascular complications at 18-F sheath insertion sites, the subclavian group displayed a significantly lower rate of life-threatening (p = 0.05), major (p = 0.04), and minor (p = 0.02) (Fig. 2) bleeding events.

Rates of new permanent pacemaker implantation and of new left bundle branch block were similar between groups,

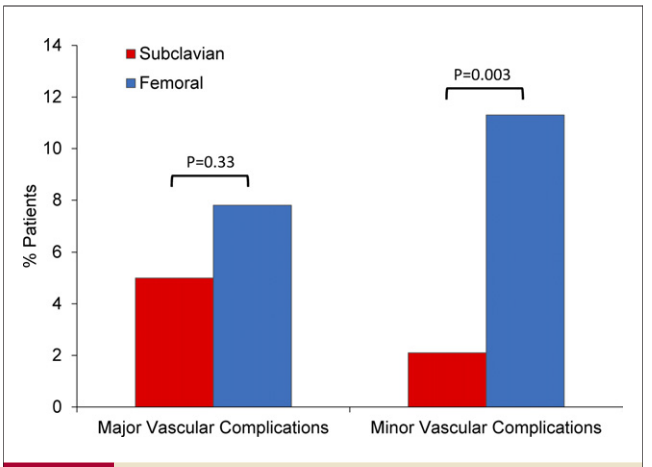

Figure 1 Vascular Complications

Major and minor vascular complications related to the 18-F access.

as well as the rate of more than mild paravalvular leak (17.9% vs. 17.7%; p = 0.91).

30-day outcome. Thirty-day outcomes were available for all patients and are defined in Table 4. All-cause mortality (p = 0.80) and cardiovascular mortality (p = 0.79) were similar between groups. The combined safety endpoint (all-cause mortality, major stroke, life-threatening bleeding, acute kidney injury/stage 3, myocardial infarction, major vascular complication, and reintervention for valve-related dysfunction) was also similar between subclavian and femoral patients (p = 0.26).

Long-term outcome. Two-year follow-up data were available in 95.7% of patients, with survival status reported as of September 30, 2011. Median follow-up in the subclavian and femoral groups was 17 (range 8 to 27) months and 20 (range 8 to 31) months, respectively. The Kaplan-Meier survival curve for the 2 groups is shown in Figure 3. Survival

Table 3 In-Hospital Outcome

Outcome	Subclavian Access	Femoral Access	p Value
All-cause mortality	7 (5.0)	6 (4.3)	0.78
Stroke	3 (2.1)	3 (2.1)	0.99
Myocardial infarction	0 (0)	0 (0)	0.99
Major vascular complications	7 (5.0)	11 (7.8)	0.33
Minor vascular complications	10 (7.1)	17 (12.1)	0.16
18-F access-related	3 (2.1)	16 (11.3)	0.003
Life-threatening bleeding events	11 (7.8)	8 (5.7)	0.48
18-F vascular complication–related	1 (0.7)	6 (4.3)	0.05
Major bleeding events	51 (36.2)	43 (30.5)	0.31
18-F vascular complication–related	4 (2.8)	12 (8.5)	0.04
Minor bleeding events	13 (9.2)	12 (8.5)	0.83
18-F vascular complication–related	1 (0.7)	8 (5.7)	0.02
Acute kidney injury/stage 3	6 (4.3)	14 (9.9)	0.02
New left bundle branch block	35 (24.8)	30 (21.3)	0.49
New permanent pacemaker	34 (24.1)	33 (23.4)	0.88

Values are n (%).

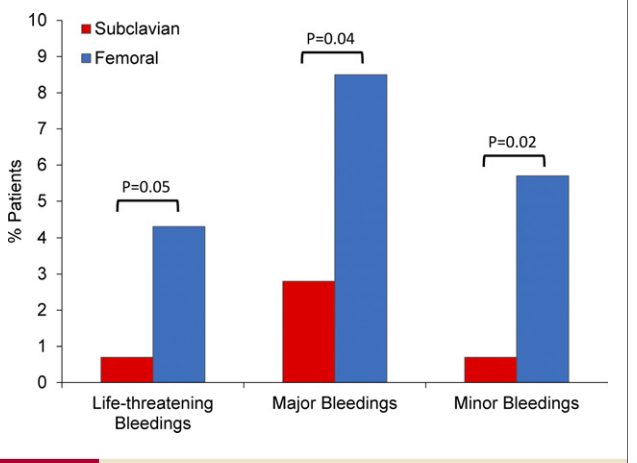

Figure 2 Bleeding Complications

Bleeding events related to vascular complications at the site of 18-F access.

Table 4 Clinical Outcomes at 30 Days

Outcome	Subclavian Access	Femoral Access	p Value
All-cause mortality	8 (5.7)	9 (6.4)	0.80
Cardiac mortality	8 (5.7)	7 (5.0)	0.79
Cardiac rehospitalization	2 (1.4)	2 (1.4)	0.99
Stroke	3 (2.1)	3 (2.1)	0.99
Myocardial infarction	0 (0)	0 (0)	0.99
Aortic valve reintervention	0 (0)	1 (0.7)	0.31
Combined safety endpoint	28 (19.9)	36 (25.5)	0.26
New pacemaker	35 (24.7)	35 (24.7)	0.99

Values are n (%).

at 2 years was 74.0 ± 4.0% in the subclavian group compared with 73.7 ± 3.9% in the femoral group (p = 0.78). The 2-year freedom from cardiovascular death was 87.2 ± 3.1% versus 88.7 ± 2.8% in the subclavian versus femoral group, respectively (p = 0.84) (Fig. 4). Between 30 days and 2 years, 3 subclavian and 2 femoral patients underwent aortic valve reintervention; 14 subclavian and 10 femoral patients required rehospitalization for cardiac causes; 2 femoral patients developed prosthetic valve dysfunction; and 1 subclavian patient required pacemaker implantation. The 2-year freedom from the combined efficacy endpoint (all-cause mortality after 30 days, hospitalization for valve-related or cardiac decompensation, and prosthetic valve dysfunction) was 71.7 ± 4.3% versus 71.4 ± 4.1% in the subclavian versus the femoral group, respectively (p = 0.78) (Fig. 5).

Discussion

This is the first report to the best of our knowledge on the medium-term results of TAVI with the CoreValve through the subclavian access in the largest cohort of patients described so far. Importantly, the subclavian population was compared with a propensity-matched femoral cohort of patients.

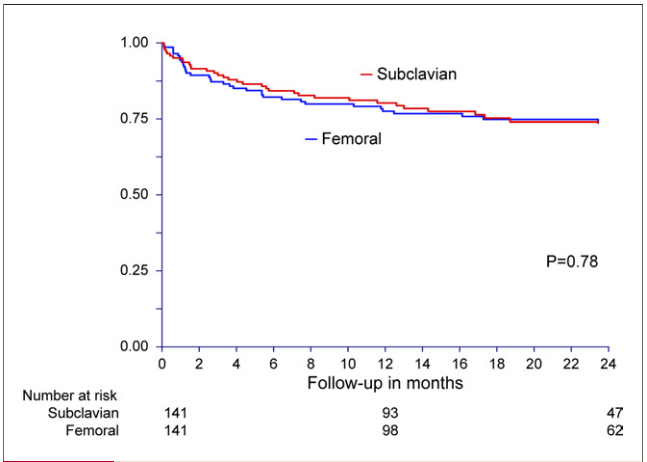

Figure 3 Kaplan-Meier Estimates of 2-Year Survival

Red line = subclavian group; **blue line** = femoral group.

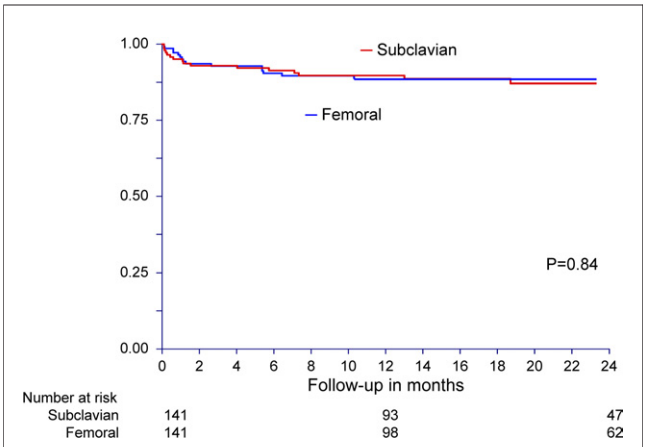

Figure 4 Freedom From Cardiovascular Death

Kaplan-Meier estimates of 2-year freedom from cardiovascular death.
Red line = subclavian group; **blue line** = femoral group.

Peripheral artery disease, ranging from 19% to 42% in patients undergoing TAVI (4,8–10), often makes the femoral access difficult or even impossible. Thus, alternative access routes have been proposed; namely, the transapical (1), subclavian/axillary (2), and direct aortic access (3).

We previously reported the early results of the subclavian access in the initial 54 patients from the Italian CoreValve Registry, demonstrating excellent procedural success, low in-hospital complications, and good 6-month survival (2). In the current study, we report the 2-year results in a tripled subclavian population compared with a propensity score–matched femoral population. In fact, patients with contraindications to the femoral access usually experience more comorbidities and have a higher surgical risk (2,11).

Procedural results. Procedural success was excellent in both groups, confirming that TAVI can be performed

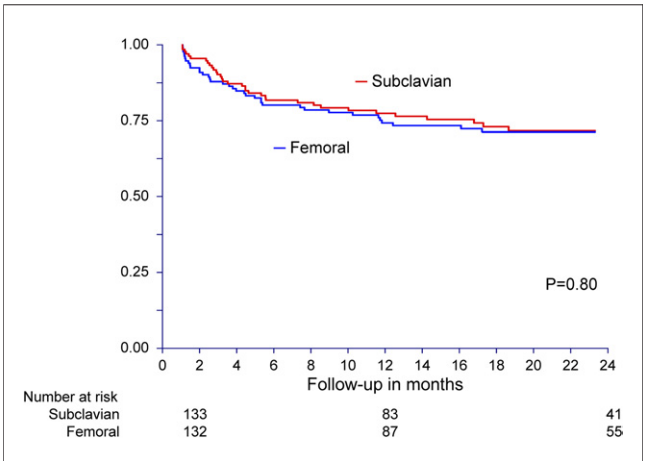

Figure 5 Freedom From Combined Efficacy Endpoint

Kaplan-Meier estimates of 2-year freedom from combined efficacy endpoint.
Red line = subclavian group; **blue line** = femoral group.

through the subclavian route without additional procedural risks. Although technically more demanding, the right subclavian access was successful in 6 of 6 patients. The technique used for the subclavian access was uniform, with direct puncture of the artery in 95.7% of the cases. Importantly, use of local anesthesia rose from 25.0% in the first 4 cases per center to 56.2% subsequently ($p = 0.004$). The possibility of using local anesthesia is an important advantage over the transapical and direct aortic access, considering the risks of general anesthesia in elderly patients who suffer from multiple comorbidities (6).

Vascular complications. The large-bore arterial sheaths required for TAVI entail a relevant risk of vascular access complications, which have an important negative impact on outcome (4,10). The development of lower profile devices allowed for a decrease in vascular complications with respect to the initial experience; however, the rate of major vascular injuries in contemporary TAVI registries ranges from 2.0% to 22.9%, depending on the definitions used (4,8,12). The standardization of endpoint definitions recently proposed by the Valve Academic Research Consortium represents a cornerstone for current and future studies (7) and was adopted in the Italian CoreValve Registry soon after its publication. In our study, the incidence of major and minor vascular complications was acceptably low and similar between subclavian and femoral patients. However, minor vascular complications related to the 18-F access were significantly lower in the subclavian group ($p = 0.003$). Similarly, when considering only bleeding events related to an 18-F site complication, the rates of all types of bleeding events were significantly lower in the subclavian group. These findings demonstrate the safety of this approach, which can be accomplished without increased risks of vascular injury and bleeding.

Early and long-term outcome. In-hospital and 30-day adverse events were low in both groups, including mortality, stroke, and myocardial infarction. The rate of new permanent pacemaker implantation was also similar between groups. Of notice, subclavian patients displayed a significantly lower rate of acute kidney injury/stage 3 ($p = 0.02$), probably related to the higher amount of contrast medium administered with the femoral approach due to the need for angiographic control of the iliofemoral arteries.

The 2-year Kaplan-Meier survival was ~74% in both groups, which is within the 61.9% to 73.7% range reported in the literature (8,13). This finding demonstrates that the choice of the subclavian access did not negatively affect long-term survival. Importantly, the 2-year survival in our subclavian TAVI experience compares favorably with the 63.3% survival reported for the nontransfemoral cohort (>85% transapical) of the UK TAVI registry. In addition, the transapical approach is definitely more invasive, mandates general anesthesia, and entails additional specific risks, including chest re-exploration, left ventricular false aneurysm, and apical akinesia (11).

Our survival data showed a marked attrition in the first 6 months after TAVI, in addition to 30-day mortality, which is in agreement with most studies (5,8–11). This flattening of the Kaplan-Meier curve after 6-month post-intervention was more evident regarding freedom from cardiovascular death, which was high in both groups at 2 years ($87.2 \pm 3.1\%$ vs. $88.7 \pm 2.8\%$; $p = 0.84$). Such discrepancy between all-cause and cardiovascular mortality is frequently reported in TAVI patients (5,9) who often have severe comorbidities that may lead to death even a few months after TAVI. Further investigation is warranted to prospectively identify those candidates who have dismal short-term prognosis, independent of their aortic valve stenosis.

Study limitations. The Italian CoreValve registry has independent monitoring and event adjudication; however, data are self-reported and have not been systematically validated. In addition, the data were re-evaluated to conform to the Valve Academic Research Consortium criteria. Finally, the comparison between the subclavian and femoral cohorts was propensity matched but not randomized.

Conclusions

Outcomes after TAVI through the subclavian access in this high-risk population were encouraging and similar to those of TAVI through the femoral approach. In addition, vascular and bleeding complications directly related to the 18-F arterial access were lower in the subclavian cohort, and no specific subclavian complication was observed. These results suggest that the subclavian access represents a valid alternative not only when the femoral access is contraindicated but also when it appears difficult, albeit feasible.

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