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Transaxillary compared with transcarotid access for TAVR: a propensity-matched comparison from a French multicentre registry

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KEYWORDS

- aortic stenosis
- other
- subclavian
- TAVR

Abstract

Aims: No randomised study comparing the outcomes of transcarotid (TC) and transaxillary (TAx) TAVR has been conducted to date. The purpose of this study was to understand which approach should be the preferred alternative by comparing their outcomes using a propensity-matched comparison in a French multicentre registry.

Methods and results: From 2010 to 2018, a French multicentre prospective registry included 502 patients, with 374 undergoing TC-TAVR and 128 TAx-TAVR for symptomatic aortic stenosis. Patients treated through TAx access were matched 1:2 with patients treated through the TC route by using a propensity score (20 clinical, anatomical and procedural variables) and by date of the procedure. The first outcome was mortality at one-month follow-up. The second outcome was one-month stroke/transient ischaemic attack (TIA). In propensity-matched analyses, the incidence of the primary outcome was similar in the TAx and TC groups (TAx 5.5% vs TC 4.5%, OR 1.23, 95% CI: 0.40-3.70). The secondary outcome was similar in TAx (3.2%) and TC (6.8%, OR 0.52, 95% CI: 0.14-1.84). Minor bleeding (2.7% vs 9.3%, OR 0.26, 95% CI: 0.07-0.92) and main access haematoma (3.6% vs 10.3%, OR 0.034, 95% CI: 0.09-0.92) were significantly more frequent with the TC access. One-month clinical efficacy and safety and one-year mortality did not differ according to the different routes.

Conclusions: One-month mortality, one-month stroke/TIA and one-year mortality are similar with TAx-TAVR and TC-TAVR. However, TC-TAVR is accompanied by more minor bleeding and main access haematoma compared with the transaxillary route.

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Abbreviations

AKI	acute kidney injury
AR	aortic regurgitation
CA	carotid artery
CABG	coronary artery bypass grafting
COPD	chronic obstructive pulmonary disease
GA	general anaesthesia
MSCT	multislice computed tomography
MRI	magnetic resonance imaging
PCI	percutaneous coronary intervention
SAVR	surgical aortic valve replacement
TAVR	transcatheter aortic valve replacement
TAx	transaxillary/subclavian
TC	transcarotid
TIA	transient ischaemic attack
TTE	transthoracic echocardiography
VARC-2	Valve Academic Research Consortium-2

Introduction

The transfemoral (TF) access is the primary access route for the vast majority of patients undergoing transcatheter aortic valve replacement (TAVR) thanks to the refinement of the procedure and material[1]. In 2019, the penetration of the transfemoral approach was as high as 85% in the USA[2] and France[3], and 99% in low-risk patients[4].

The optimal access route for patients undergoing TAVR who are not candidates for a TF approach has not been clearly elucidated[5,6]. The use of the transapical and transaortic techniques has been surpassed by other routes[7]. Possible extrathoracic alternatives for patients not amenable to TF-TAVR have been developed recently, including the transcarotid (TC) and transaxillary/subclavian (TAx) routes.

Recent studies on TAx access have reported similar outcomes, including life-threatening bleeding rates (12%) and 30-day mortality rates (6%), compared to TF procedures[8,9]. The TAx pathway also has lower 30-day mortality and shorter lengths of hospital stay than transthoracic routes including transapical and transaortic access[10-12]. However, some authors suggest that the TAx route may have a higher stroke rate[11,13] and more vascular complications[13] than TF access. We previously investigated the safety and feasibility of transcarotid TAVR using self-expanding and balloon-expandable prostheses, managed under general anaesthesia or a minimally invasive strategy with favourable clinical outcomes[14-17]. We currently use TC or TAx access as the first-line alternative approach for TAVR whenever the TF access is precluded.

The purpose of this study was to understand which approach should be the preferred alternative by comparing their outcomes using a propensity-matched comparison in a French multicentre registry.

Methods

PATIENT SELECTION

Between 2010 and 2018, consecutive patients undergoing TC and TAx TAVR at four French institutions (Institut Coeur-Poumons, CHU Lille, Lille, France; Hôpital Marie Lannelongue, Le Plessis-Robinson, France; CHU Montpellier, Montpellier, France; CH Lens, Lens, France) were included in a collaborative prospective registry. In all cases, the TF approach was precluded by diseased descending aorta (aortic dissection, aortic aneurysm, porcelain aorta), severe peripheral arterial disease (small calibre ≤5.5 mm, severely tortuous, heavily calcified, dissected, significant stenosis), or prior iliofemoral intervention or surgery. Selection of alternative access was then individualised to each patient's anatomic features and comorbidities.

The yearly number and proportions of the total number of TAVR cases that were not TF in the four participating centres (2010-2018) are shown in **Figure 1**, representing around 10% of the total number of TAVR procedures in these institutions. The mean case volume per site per year was 4.0 for TAx and 11.6 for TC procedures.

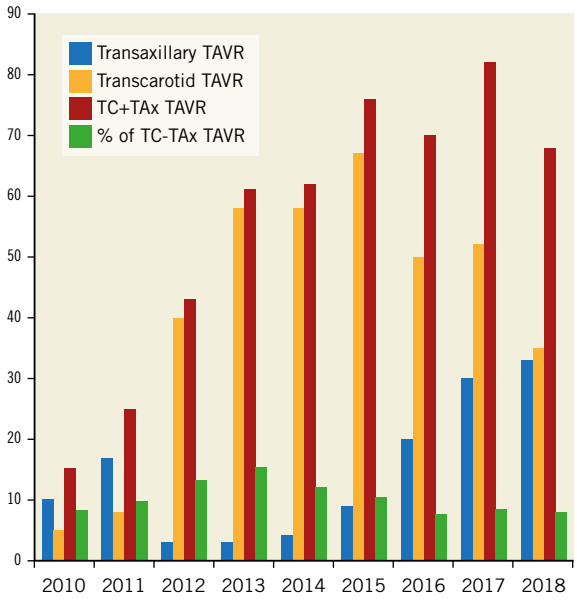

Figure 1. *Yearly number and proportion of total transcarotid (TC) and transaxillary/subclavian (TAx) TAVR procedures.*

Details concerning preprocedural screening and procedural technique can be found in **Supplementary Appendix 1** and **Supplementary Appendix 2**.

CLINICAL ENDPOINTS

The primary endpoint of interest was one-month mortality[18] in TC-TAVR and TAx-TAVR.

Secondary endpoints were one-month stroke/transient ischaemic attack (TIA), one-month clinical efficacy (all-cause mortality, disabling or non-disabling stroke, or hospitalisations for valve-related symptoms or worsening congestive heart failure [CHF]), one-month early safety (all-cause mortality, stroke [disabling and non-disabling], life-threatening bleeding, acute kidney injury [AKI], coronary artery obstruction requiring intervention, major

vascular complications, valve-related dysfunction requiring repeat procedure), and one-year mortality. Further analyses involved major outcomes including AKI, aortic regurgitation, bleeding or vascular access complications according to the Valve Academic Research Consortium-2 (VARC-2) consensus definitions[18].

All medical files were carefully reviewed and, in case of doubt, clinical events were adjudicated by a medical committee of two physicians.

STATISTICAL ANALYSIS

Quantitative variables are expressed as means (standard deviation) in the case of normal distribution or medians (interquartile range) otherwise. Categorical variables are expressed as numbers (percentages). Normality of distribution was assessed using histograms and the Shapiro-Wilk test. Patients were divided into two groups according to the TAVR access site (TAx vs TC). Baseline characteristics were described for the two study groups and the magnitude of the between-group differences was assessed by calculating the absolute standardised difference; an absolute standardised difference >10% was interpreted as a meaningful difference.

Details of the propensity-matched comparison can be found in **Supplementary Appendix 3**[19].

Statistical testing was conducted at the two-tailed α level of 0.05. Data were analysed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

POPULATION

The number of TC and TAx procedures are shown in **Figure 1**, and the study flow chart is shown in **Figure 2**.

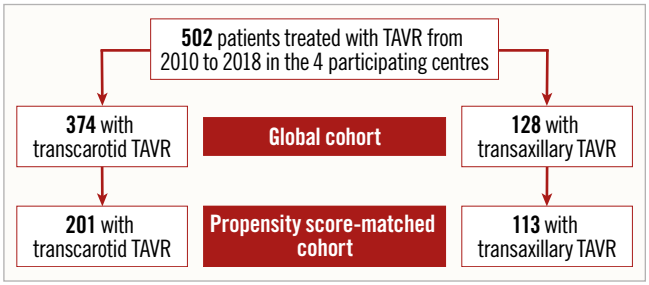

Figure 2. *Study flow chart.*

Baseline characteristics before matching and handling missing values are presented in **Supplementary Table 1**. Baseline characteristics according to access, before and after propensity score matching and after handling missing values by multiple imputation are presented in **Table 1**. The distributions of propensity score according to access are reported in **Supplementary Figure 1**. Absolute standardised differences between TAVR routes before and after propensity score matching are reported in **Supplementary Figure 2**.

Before matching, most characteristics were already well balanced (absolute standardised difference ≤10%), except that patients treated with a TAx-TAVR had a higher prevalence of severe iliofemoral disease, severe renal dysfunction, and chronic obstructive pulmonary disease (COPD). TAx-TAVR procedures were more often performed after 2015, with a second-generation prosthesis (SAPIEN 3 [S3; Edwards Lifesciences, Irvine, CA, USA] and Evolut™ R [Medtronic, Minneapolis, MN, USA]), with more predilation and using the right access more frequently. These differences were controlled after propensity score matching **(Table 1, Supplementary Figure 2)** where 113 TAx-TAVR cases could be matched with 201 TC-TAVR cases.

IMPACT OF ACCESS SITE ON THE OUTCOMES

(i) MORTALITY AND COMPOSITE OUTCOMES

In the propensity score-matched cohort, there was no difference in one-month mortality (TAx 5.5% vs TC 4.5%, odds ratio [OR] 1.23, 95% confidence interval [CI]: 0.40-3.70), one-month early safety (TAx 88.6% vs TC 85.8%, OR 1.38, 95% CI: 0.64-2.94) or clinical efficacy (TAx 88.6% vs TC 85.9%, OR 1.22, 95% CI: 0.57-2.58) between the two access sites **(Table 2)**. There was also no difference in mortality at one-year follow-up, with a matched hazard ratio (HR) of 0.83 (95% CI: 0.41-1.70).

(ii) MORBIDITY INCLUDING VASCULAR COMPLICATIONS

Among procedural and in-hospital events, major vascular access complications, and life-threatening and major bleeding occurred at the same rate in the two groups. Lower rates of minor bleeding (TAx 2.7% vs TC 9.3%, OR 0.26, 95% CI: 0.07-0.92) and main access haematoma (TAx 3.6% vs TC 10.3%, OR 0.29, 95% CI: 0.09-0.92; p=0.034) were also found in patients treated through the TAx route, while the difference in minor vascular access complications did not reach the significance level (TC 7.0% vs TAx 2.7%, OR 0.31, 95% CI: 0.08-1.15; p=0.078). There was no significant difference in post-procedural mean transprosthetic maximal velocity between the two groups (mean difference between TAx and TC=0.10; 95% CI: −0.08-0.29).

(iii) CEREBROVASCULAR EVENTS

Overall, there were 30 (6.0%) VARC-2-defined one-month cerebrovascular events (16 [3.2%] strokes [NIHSS score 1 n=1, 2 n=1, 3 n=3, 4 n=3, 5 n=3, 6 n=4, and 8 n=1] and 14 [2.8%] TIAs), as assessed by clinical and neuroimaging criteria. Nine patients with stroke (56%) had no sequelae at hospital discharge. Cerebrovascular events happened shortly after the procedure (n=15 at day 0, n=5 at day 1, n=2 at day 2, n=3 at day 3, n=2 at day 5, n=2 at day 6, n=1 at day 11). The clinical deficits were localised as ipsilateral (n=8) or contralateral (n=12) to the vascular access site. Clinical features of the events included confusion (n=4), hemiparesis (n=4), hemiplegia (n=15) and aphasia (n=5), and Claude Bernard-Horner signs (n=2); neuroimaging showed new ischaemic lesions in the 16 stroke cases (multiple embolic lesions). One patient (0.8%) in the TAx group had a brachial plexus sideration. After propensity matching, the one-month stroke/TIA rate did not differ between the two groups (TAx 3.2% vs TC 6.8%, OR 0.52, 95% CI: 0.14-1.84).

Table 1. Main baseline characteristics in patients with transcatheter aortic valve replacement (TAVR) according to access site before and after propensity score matching.

Characteristics		Before matching			After matching		
		Transcarotid TAVR (n=374)	Transaxillary TAVR (n=128)	ASD, %	Transcarotid TAVR (n=201)	Transaxillary TAVR (n=113)	ASD, %
Patient characteristics							
Age, years, median (IQR)		83 (77-86)	82 (79-86)	1.2*	83 (77-87)	82 (78-86)	2.2*
Male gender		223 (59.6)	80 (62.5)	5.9	126 (62.7)	70 (62.2)	1.2
Diabetes mellitus		122 (32.6)	36 (28.1)	9.8	63 (31.4)	33 (28.8)	5.6
Iliofemoral artery disease		227 (60.7)	88 (68.8)	16.9	135 (67.4)	77 (68.4)	2.1
Previous PCI		233 (62.3)	81 (63.3)	2.0	119 (59.2)	72 (63.8)	9.4
Previous CABG		68 (18.2)	27 (21.1)	7.3	37 (18.6)	21 (18.6)	0.2
Previous AVR		27 (7.2)	7 (5.5)	7.2	12 (6.2)	6 (5.4)	3.4
Severe renal dysfunction		137 (36.6)	64 (50.0)	27.2	91 (45.3)	50 (44.1)	2.3
COPD		111 (29.8)	50 (39.1)	19.9	78 (38.6)	43 (37.8)	1.4
Prior stroke/TIA		58 (15.6)	14 (10.9)	13.5	26 (13.1)	12 (10.8)	6.8
STS score (2018), %, median (IQR)		5.4 (3.6-8.3)	5.8 (3.9-8.6)	8.7*	5.5 (3.5-8.1)	5.8 (3.9-8.5)	8.6*
TTE characteristics							
LVEF, %, median (IQR)		55 (45-60)	55 (45-61)	0.1*	55 (41-60)	55 (45-61)	8.1*
Procedural characteristics							
Intervention after 2015		201 (53.7)	91 (71.1)	36.4	132 (65.9)	77 (67.9)	4.4
Right access		66 (17.6)	30 (23.4)	14.4	41 (20.5)	24 (21.3)	1.9
Predilation		135 (36.1)	71 (55.5)	39.6	104 (51.6)	55 (48.6)	6.0
Post-dilation		54 (14.4)	17 (13.3)	2.8	25 (12.4)	16 (14.1)	5.2
Valve-in-valve		29 (7.8)	6 (4.7)	12.7	11 (5.6)	6 (5.4)	0.6
Local anaesthesia		77 (20.6)	6 (4.7)	49.3	11 (5.6)	6 (5.4)	0.1
Bioprosthesis size	23 mm	43 (11.5)	22 (17.3)	24.6	29 (14.2)	16 (14.5)	10.7
	26 mm	132 (35.3)	50 (39.3)		77 (38.3)	43 (37.4)	
	29 mm	170 (45.5)	49 (38.0)		85 (42.1)	47 (41.8)	
	31 or 34 mm	29 (7.8)	7 (5.5)		10 (5.4)	7 (6.3)	
2nd generation devices		182 (48.7)	91 (71.1)	47.0	134 (66.7)	77 (67.9)	2.6

Values expressed as numbers (%) unless otherwise indicated. Values were calculated after handling missing data using multiple imputation procedure. * Estimated using the rank-transformed data. Severe renal dysfunction defined as GFR ≤30 ml/min/m². 2nd generation devices included SAPIEN 3 and Evolut R prostheses. AR: aortic regurgitation; ASD: absolute standardised difference; AVR: aortic valve replacement; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; GFR: glomerular filtration rate; IQR: interquartile range; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; TAVR: transcatheter aortic valve replacement; TIA: transient ischaemic attack; TTE: transthoracic echocardiography

Discussion

Here we describe one of the largest series of patients undergoing TC or TAx vascular access for TAVR. The main findings from this propensity-matched cohort are: (i) TC-TAVR and TAx-TAVR have similar one-month mortality, one-month stroke/TIA, and clinical safety and efficacy with balloon-expandable or self-expanding valves, and (ii) less minor bleeding and main access haematoma occur in the TAx access group.

Comparative data about these two most currently used alternative routes for TAVR are unavailable. Numerous articles have previously described these routes in comparison to transthoracic TAVR with favourable results **(Table 3)**.

NON-FEMORAL PERIPHERAL TAVR

A recent French registry in a non-femoral peripheral TAVR cohort found a similar stroke rate (3.35%), lower major vascular complications (0.68%) and higher major bleeding (8.56%)[20] compared to our analysis. We also report device success (95.4%) and one-month mortality (5.0%) rates similar to those reported by Dahle et al[11]. However, this STS/ACC registry[11] using only balloon-expandable valves reported extremely low major vascular complications (1.1%) and life-threatening bleeding rates (0.1%). Evaluation of VARC-2 outcomes was not clinically adjudicated in these registries[11,16,20]. Also, it cannot be excluded that some clinical events, in particular TIA, might have been partly underreported, since

Table 2. Procedural, hospital, 1-month and 1-year outcomes in patients with transcatheter aortic valve replacement according to access site after propensity score matching.

Outcomes	Transcarotid TAVR (n=201)	Transaxillary TAVR (n=113)	Effect size (95% CI)	*p*-value
Procedural and in-hospital outcomes				
Device success	192 (95.4)	108 (95.5)	0.95 (0.28-3.16)*	0.93
Acute kidney injury 2-3	27 (13.5)	25 (22.5)	1.72 (0.90-3.27)*	0.10
New pacemaker implantation	38 (19.0)	22 (19.5)	0.99 (0.53-1.81)*	0.97
LT or major bleeding	11 (5.7)	4 (3.6)	0.62 (0.18-2.13)*	0.44
Minor bleeding	19 (9.3)	3 (2.7)	0.26 (0.07-0.92)*	0.035
Major vascular access complications	17 (8.5)	10 (9.0)	1.20 (0.48-2.96)*	0.70
Minor vascular access complications	14 (7.0)	3 (2.7)	0.31 (0.08-1.15)*	0.078
Main access haematoma	21 (10.3)	4 (3.6)	0.29 (0.09-0.92)*	0.034
Hospital stay, days, median (IQR)	8 (6-11)	9 (6-13)	0.84 (0.67-1.05)**	0.12
AR grade ≥II	19 (9.3)	6 (5.4)	0.54 (0.20-1.45)*	0.22
Transprosthetic maximal velocity, m/s, mean (SD)	2.1 (0.8)	2.2 (0.9)	0.10 (-0.08-0.29)#	0.25
1-month and 1-year outcomes				
1-month mortality	9 (4.5)	6 (5.5)	1.23 (0.40-3.70)*	0.71
1-month clinical efficacy	173 (85.9)	100 (88.6)	1.22 (0.57-2.58)*	0.61
1-month safety	172 (85.8)	100 (88.6)	1.38 (0.64-2.94)*	0.40
1-month stroke/TIA	14 (6.8)	4 (3.2)	0.52 (0.14-1.84)*	0.31
1-year all-cause mortality, n (KM, %)	23 (19.1)	16 (16.1)	0.83 (0.41-1.70)§	0.62

Values are number of events (%) unless otherwise indicated. Number of events (%), mean (SD) and effect sizes were calculated after handling missing values for variables included in the propensity score and outcomes by multiple imputation (n=10). * Odds ratios calculated using a GEE model for binary data with a logit link function. ** Subhazard ratio calculated using a Fine and Gray regression model with alive at discharge as outcome event and intra-hospital mortality as competing event, with the robust sandwich variance estimate to account for the matched sets. # Mean between-group difference calculated using linear mixed model including matched sets as random effect. § Hazard ratio calculated using a Cox regression model with the robust sandwich variance estimate to account for the matched sets. Clinical efficacy defined as all-cause mortality, disabling or non-disabling stroke, or hospitalisations for valve-related symptoms or worsening congestive heart failure (CHF). Early safety defined as all-cause mortality, stroke (disabling and non-disabling), LT bleeding, acute kidney injury, coronary artery obstruction requiring intervention, major vascular complication, valve-related dysfunction requiring repeat procedure. AR: aortic regurgitation; IQR: interquartile range; KM: Kaplan-Meier estimate; LT: life-threatening; SD: standard deviation; TAVR: transcatheter aortic valve replacement; TIA: transient ischaemic attack

Table 3. Summary of recent studies with transcarotid and/or transaxillary TAVR.

Study	Access	N. TAx or TC TAVR (and TC)	Prosthesis	Results for TAx or TC
Overtchouk et al. *JACCi* (2019)[16]	TC only	314 (314)	Balloon-expandable (SAPIEN 3)	SAPIEN 3 device is safe and effective
Watanabe et al. *Circ J* (2018)[17]	TC vs TF	83 (83)	Balloon-expandable and self-expanding	Feasibility and 30-day safety are similar
Chamandi et al. *Circ Cardiovasc Interv* (2018)[7]	TC vs Tap/Tao	101 (101)	Balloon-expandable and self-expanding	Less atrial fibrillation, major bleeding, acute kidney injury and shorter length of stay
Gleason et al. *Ann Thorac Surg* (2018)[9]	TAx vs TF	202 (0)	Self-expanding	Similar morbidity and mortality rates
Beve et al. *Am J Cardiol* (2019)[12]	TAx+TC vs Tao+Tap	87 (14)	Balloon-expandable and self-expanding	Shorter length of stay Comparable mortality and morbidity
Dahle et al. *JACCi* (2019)[11]	TAx vs Tap+Tao	1,249 (0)	Balloon-expandable	Lower 30-day mortality, shorter length of stay, higher stroke rate
Amer et al. *Ann Thorac Surg* (2019)[22]	TAx vs TC	71 (33)	Balloon-expandable and self-expanding	Shorter fluoroscopy time with TC
Van der Wulp et al. *Ann Thorac Surg* (2019)[24]	TAx only	362 (0)	Self-expanding	5% mortality at 1 month
Debry et al. *EuroIntervention* (2020; current study)	TAx vs TC	502 (374)	Balloon-expandable and self-expanding	Similar 1-month mortality and 1-month stroke/TIA rate, more minor bleeding and vascular access complications with TC

Tao: transaortic; Tap: transapical; TAx: transaxillary; TC: transcarotid; TF: transfemoral

they are also significantly lower than reported in clinical trials[21]. We report similar rates of major vascular complications (9.0% vs 11.9%) and less major and life-threatening bleeding (3.6% vs 11.4%) compared to previous TAx studies[9,13] with only self-expanding valves. Potential explanations for this detrimental result with non-femoral TAVR include a procedural learning curve. The TAx or TC access may also be more delicate than iliofemoral ones and prone to vessel dissection, stenosis or thrombosis, and is not accessible for effective manual compression.

COMPARISON OF TAx-TAVR AND TC-TAVR

In line with a previous report[22], our study suggests that both approaches are equally safe without difference in early (30-day) and late (one-year) mortality and with similar early stroke/TIA rates. In the case of TC-TAVR, even if it offers a more direct (straighter) access, a less angular path to reach the aortic valve, with less vascular interaction, local complications including local haematoma and minor bleeding, debris embolisation, and the transient reduction in cerebral blood flow during the procedure may explain the non-significant increase in the one-month stroke/TIA rate (6.8% vs 3.2%). The TIA/stroke rate with the TC route did not decrease significantly between the early period (2010-2015 and the use of first-generation prostheses) and after 2015 (7.0% vs 5.4%, p=0.53). The rate of 30-day stroke/TIA that we report is in the upper margin of those previously reported by Amer et al[22] (3%), and Mylotte et al[15] (3.2%). These figures are also consistent with those of a previous report of ours in which a 5.7% rate of periprocedural cerebrovascular events and an 11.4% rate of global vascular access complications with TC-TAVR were reported[14]. Passive antegrade carotid perfusion with a temporary femoro-carotid shunt during TC-TAVR was used for the first TC-TAVR patients during the early days (2010) and is no longer used.

The more direct access from the carotid artery allows more precise positioning of the prosthesis, especially for self-expanding valves, which could have resulted in a reduction in periprosthetic regurgitation. However, the angle of the delivery catheter from the carotid artery with respect to the plane of the ring is less favourable than for the left axillary artery which allows the delivery catheter to position itself on the lateral wall of the aorta and finally to cross the plane of the ring more perpendicularly than from the carotid artery **(Figure 3)**.

We also prefer the left axillary/carotid artery over the right because it avoids injury or embolisation to the innominate artery that supplies the right carotid and vertebral distribution. Also, isolated injury to the left axillary/carotid artery is easier to repair than innominate artery injury. While our rate of percutaneous TAx access is low, it remains unclear how surgical and percutaneous TAx approaches may ultimately differ as centres gain more experience with each approach[23].

The observed incidence of combined vascular and bleeding complications in both groups underscores the need for a detailed multidisciplinary preprocedural assessment of vascular anatomy to determine the optimal alternative TAVR approach.

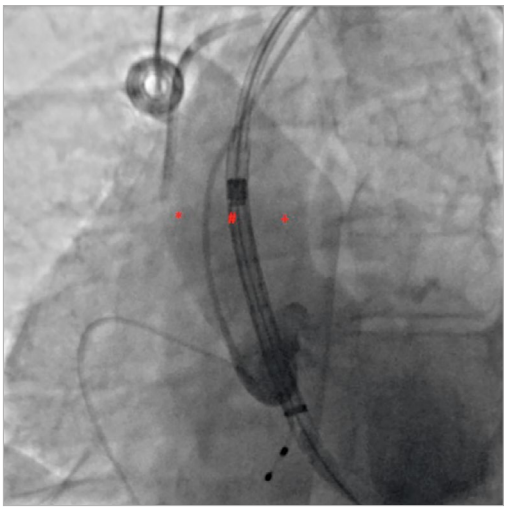

Figure 3. *Optimising the delivery of self-expanding valves according to vascular access. When using the left axillary artery, as the delivery catheter positions itself on the lateral wall of the aorta (*), it is better to open the prosthesis at 6 mm under the annulus. When using the carotid or the right axillary artery (+), delivery should start from 0 mm. When arriving at the centre of the native valve (#), and therefore perpendicular to the annulus, delivery should start 3 mm under the annulus.*

Limitations

Limitations to this study are inherent to its non-randomised design. The present findings are derived from observational analyses which are subject to well-known limitations. The first is the potential for confounding by measured or unmeasured variables, which cannot be ruled out, even after propensity score matching or adjustment. A second limitation is missing data in some covariates, including in the propensity score calculation, as well as in outcomes. Although we used multiple imputations to handle missing data as appropriate, we cannot exclude that missing data could have introduced a bias in estimates.

Conclusions

TC-TAVR and TAx-TAVR have similar one-month mortality, one-month stroke/TIA and clinical safety and efficacy with balloon-expandable or self-expanding valves. Less minor bleeding and main access haematoma occurred in the TAx access group. Randomised studies are required to ascertain whether TC-TAVR and TAx-TAVR yield similar results.

Impact on daily practice

Early post-procedural complications following alternative peripheral accesses for TAVR have dropped significantly over the years with growing experience, and are overall similar through either the TAx or TC route. However, our data may suggest that less minor bleeding and main access haematoma occur in the TAx access group.

Appendix. Study collaborators

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Preprocedural screening.

Supplementary Appendix 2. Procedural technique.

Supplementary Appendix 3. Statistical analysis.

Supplementary Figure 1. Distribution of propensity score in the transcarotid TAVR and transaxillary TAVR groups.

Supplementary Figure 2. Absolute standardised differences between transcarotid TAVR and transaxillary TAVR groups before and after propensity score matching.

Supplementary Table 1. Baseline characteristics and outcomes in patients with transcatheter aortic valve replacement (TAVR) according to access site before propensity score matching and before handling missing values by multiple imputations.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00117

Supplementary data

Supplementary Appendix 1. Preprocedural screening

Suitable carotid and axillary artery anatomy and dimensions, and vertebral artery patency were carefully assessed with preoperative Doppler ultrasound and multislice computed tomography (MSCT) as previously described [14,16]. A common carotid or axillary artery minimal luminal diameter threshold of ≥6.0 mm was considered appropriate for these vascular accesses.

Patients with significant (≥50%) common or internal carotid artery stenosis, and/or plaque considered to be at high risk of embolisation, were not considered for transcarotid TAVR. Prior ipsilateral carotid artery intervention, contralateral carotid artery occlusion, or stenosis/occlusion of the vertebral arteries were also considered to be contraindications to transcarotid TAVR.

Patients with steep subclavian to arch angulation (e.g., >80°), severe aortic root angulation or ipsilateral internal mammary artery used as a coronary bypass graft were considered to be contraindicated for transaxillary TAVR.

Supplementary Appendix 2. Procedural technique

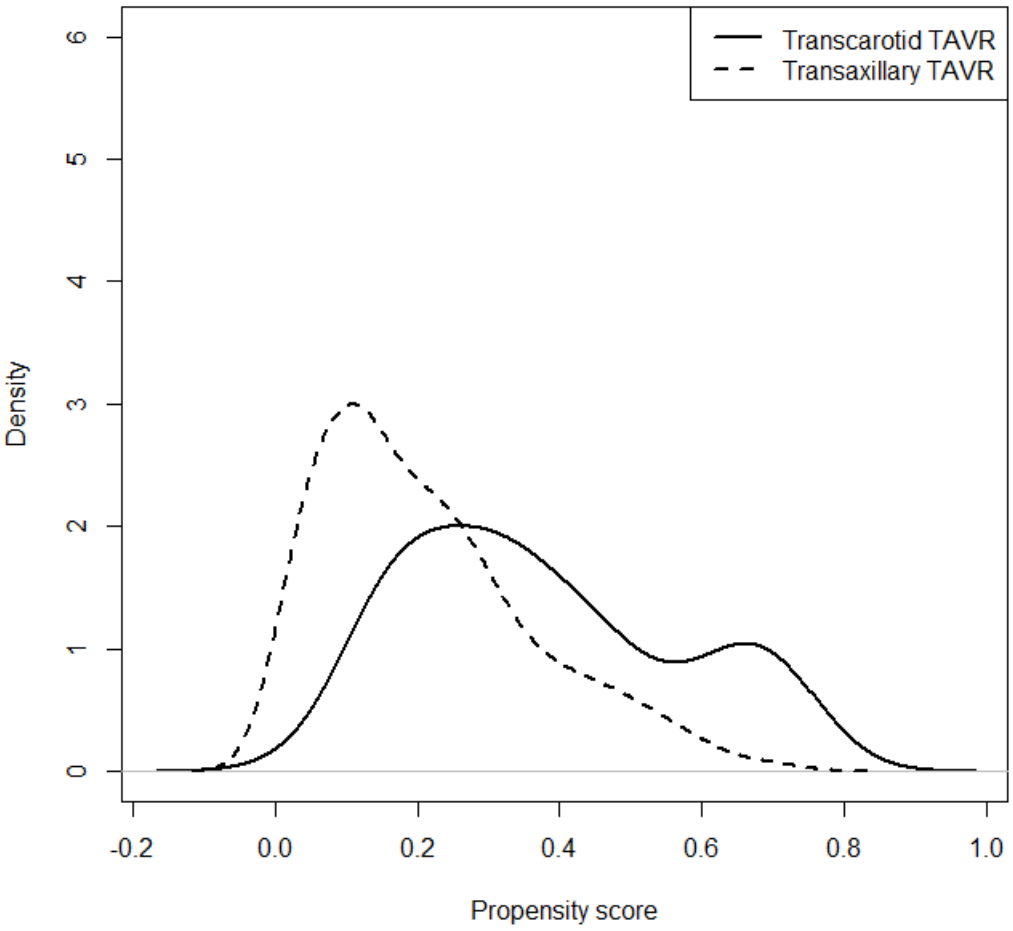
The left common carotid or left axillary artery was preferentially selected as it afforded simpler cardiac catheterisation with more favourable annular alignment, and operating room configuration. Selection of the bioprosthesis was determined following aortic root assessment using MSCT.

Standard transcarotid/transaxillary TAVR implantation technique was followed as previously described [9,10,14], with unfractionated intravenous heparin given to achieve an activated clotting time of ≥250 seconds. Surgical access with TAx was predominant as the axillary percutaneous approach is relatively recent. All patients were receiving at least single antiplatelet therapy at the time of TAVR. Procedures were performed under general or local anaesthesia with invasive haemodynamic monitoring, according to operator preference. Doppler imaging of the carotid/axillary artery was systematically performed before discharge.

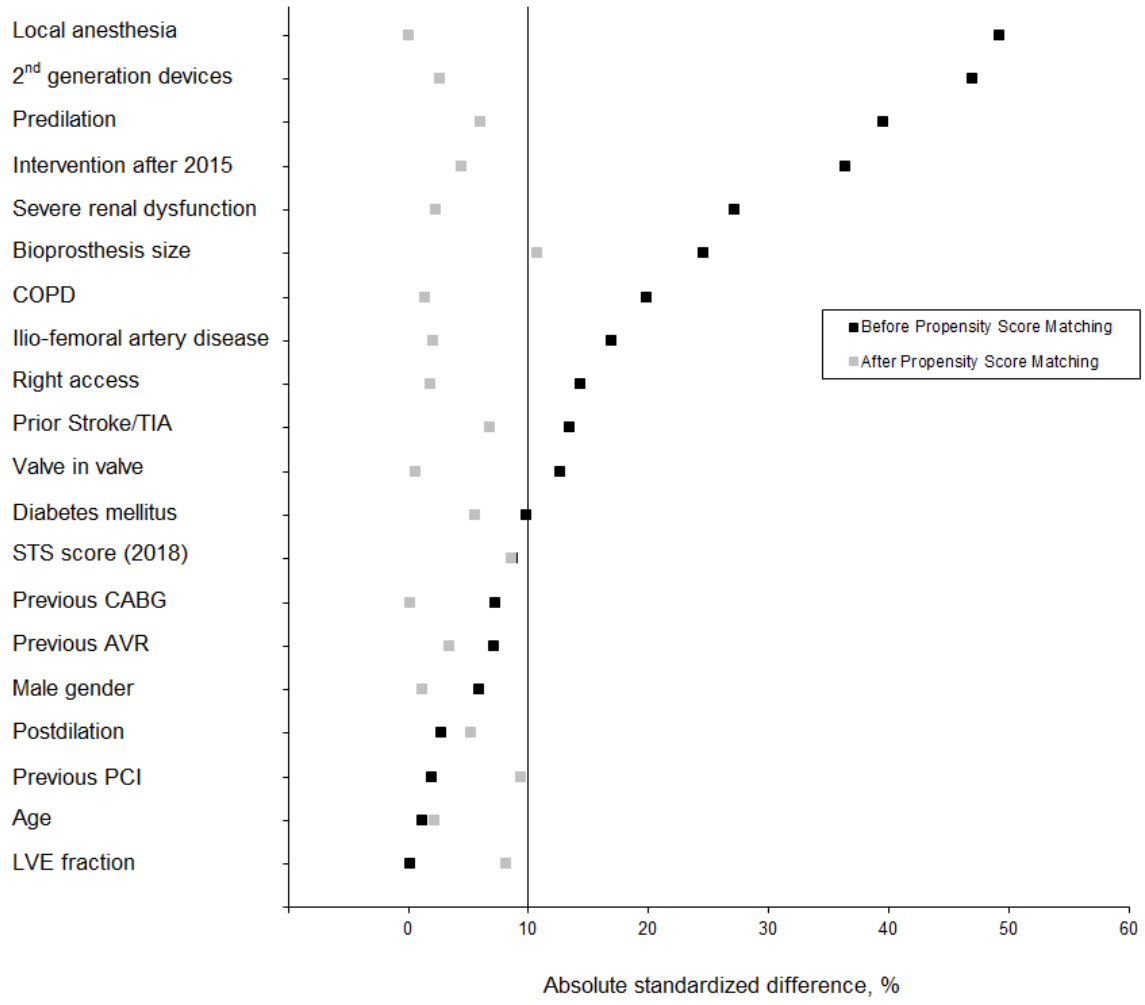
Supplementary Appendix 3. Statistical analysis

We compared the outcomes between the two study groups after taking into account the potential confounding factors by using the propensity score-matching method. The propensity score was estimated using a non-parsimonious multivariable logistic regression model, with study groups as the dependent variable and all of the characteristics listed in **Table 1** (considered as potential predictors as covariates). Patients treated by transaxillary TAVR were matched 1:2 to patients treated with transcarotid TAVR according to propensity score using the greedy nearest neighbour matching algorithm with a calliper width of 0.2 standard deviation of logit for propensity score. To evaluate bias reduction using the propensity score-matching method, absolute standardised differences were calculated after propensity score matching. Because of missing baseline and outcome data (range from 0 to 10.6%), we estimated the effect sizes in the matched propensity score cohort after handling missing covariate values by multiple imputations using a regression switching approach (chained equations with n=10 imputations). The imputation procedure was performed under the missing at random assumption using all baseline variables, study group and outcomes with a predictive mean matching method for continuous variables and logistic regression models (binary, ordinal or multinomial) for categorical variables. In each imputed data set, we calculated the propensity score and assembled a matched cohort to provide adjusted effect sizes, which were later combined by using Rubin's rules.

Between-group comparisons were done using a generalised estimating equations (GEE) model (binomial distribution, logit function) with a compound symmetry working correlation structure for binary outcomes, using the Fine and Gray regression model for hospital duration (considering alive at discharge as event of interest and by treating in-hospital death as competing risk), a linear mixed model with the matched blocks as random effect for transprosthetic maximal velocity, and a Cox regression model for one-year all-cause mortality with a robust sandwich variance estimator to account for the matched design. Using patients treated with transcarotid TAVR as reference, we derived from these regression models odds ratios (ORs) and hazard ratios (HRs) as treatment effect size measures, with their 95% confidence intervals (CIs). We assessed the proportional hazards assumption for Fine and Gray, and the Cox models using Schoenfeld residual plots.



Supplementary Figure 1. Distribution of propensity score in transcarotid TAVR and transaxillary TAVR groups.



Supplementary Figure 2. Absolute standardised differences between transcarotid TAVR and transaxillary TAVR groups before and after propensity score matching.

Supplementary Table 1. Baseline characteristics and outcomes in patients with transcatheter aortic valve replacement (TAVR) according to access site before propensity score matching and before handling missing values by multiple imputations.

	Transcarotid TAVR, n=374	Transaxillary TAVR, n=128
Patient characteristics		
Age, years, median (IQR)	83.0 (77.0 to 86.0)	82.0 (79.0 to 86.0)
Male gender	223/374 (59.6)	80/128 (62.5)
NYHA functional Class III/IV	256/374 (68.4)	99/128 (77.4)
Diabetes mellitus	122/374 (32.7)	36/128 (28.1)
BMI, kg/m², mean±SD	25 (22 to 29)	26 (24 to 29)
Iliofemoral artery disease	227/374 (60.7)	88/128 (68.8)
Coronary disease	88/374 (23.5)	47/128 (36.7)
Previous PCI	233/374 (62.3)	81/128 (63.3)
Previous CABG	68/374 (18.2)	27/128 (21.1)
Previous AVR	27/374 (7.2)	7/128 (5.5)
Severe renal dysfunction, n (%)	137/374 (36.6)	64/128 (50.0)
COPD	111/374 (29.7)	50/128 (39.1)
Atrial fibrillation	142/374 (38.0)	56/128 (43.8)
Prior stroke/TIA	58/374 (15.5)	14/128 (10.9)
Preoperative pacemaker	54/374 (14.4)	8/128 (6.3)
STS score (2018), %, median (IQR)[1]	5.3 (3.5 to 8.4)	5.8 (3.9 to 8.6)
TTE characteristics		
Transprosthetic maximal velocity, m/s, median (IQR)[2]	4.1 (4.0 to 4.7)	4.1 (3.9 to 4.6)
Aortic valve surface, cm², median (IQR)[3]	0.7 (0.6 to 0.9)	0.7 (0.6 to 0.8)
AR grade ≥II	36/373 (9.7)	8/71 (11.3)
LVEF, %, median (IQR)[4]	55 (45 to 60)	55 (45 to 61)
Procedural characteristics		
Period 2015-2018	201/374 (53.7)	91/128 (71.1)
Right access	66/374 (17.6)	30/128 (23.4)
Predilation	135/374 (36.1)	71/128 (55.5)
Post-dilation	33/321 (10.3)	17/128 (13.3)
Valve-in-valve	29/374 (7.8)	6/128 (4.7)
Need of a second valve	7/374 (1.9)	2/128 (1.6)
Local anaesthesia	77/374 (20.6)	6/128 (4.7)
Fluoroscopy time, sec, median (IQR)[5]	812 (627 to 1,147)	1,222 (848 to 1,538)
Contrast injection, ml, median (IQR)	96 (70 to 133)	105 (78 to 145)
Heparin dose, IU, median (IQR)[6]	5,000 (3,500 to 7,000)	5,000 (3,750 to 7,500)
Bioprosthesis characteristics		
Bioprosthesis size, mm		
23	43/374 (11.5)	22/127 (17.3)
26	132/374 (35.3)	50/127 (39.4)
29	170/374 (45.5)	48/127 (37.8)
31	29/374 (7.8)	6/127 (4.7)
34	0/374 (0.0)	1/127 (0.8)
Type of bioprosthesis		

Edwards SAPIEN XT	54/374 (14.4)	0/128 (0.0)
CoreValve	109/374 (29.1)	62/128 (48.4)
SAPIEN 3	137/374 (36.6)	37/128 (28.9)
Evolut R/PRO	72/374 (19.3)	28/128 (21.9)
Lotus	2/374 (0.5)	1/128 (0.8)
2nd generation devices	182/374 (48.7)	91/128 (71.1)
Outcomes		
Procedural and in-hospital outcomes		
IH mortality	17/374 (4.5)	6/128 (4.7)
Device success	357/374 (95.5)	122/128 (95.3)
Acute kidney injury 2-3	45/374 (12.0)	26/128 (20.3)
New pacemaker implantation	71/374 (19.0)	24/128 (18.8)
LT or major bleeding	17/374 (4.5)	4/128 (3.1)
Minor bleeding	31/374 (8.3)	4/128 (3.1)
Major vascular access complications	22/374 (5.9)	11/128 (8.6)
Minor vascular access complications	25/374 (6.7)	4/128 (3.1)
Main access haematoma	35/374 (9.4)	4/128 (3.1)
Hospital stay, days, median (IQR)	7 (6 to 11)	9 (6 to 13)
TTE outcomes at hospital discharge		
AR grade ≥II	29/356 (8.1)	7/128 (5.5)
Transprosthetic maximal velocity, m/s, mean (SD)	2.0±0.5	2.2±0.7
1-month outcomes		
Clinical efficacy	325/374 (86.9)	113/128 (88.3)
Early safety	321/374 (85.8)	113/128 (88.3)
Stroke/TIA	24/374 (6.4)	6/128 (4.7)
All-cause mortality	18/374 (4.8)	7 (5.5)
1-year outcome		
All-cause mortality	38/374 (10.2)	18/128 (14.1)

Values expressed as numbers (%) unless otherwise indicated. Clinical efficacy defined as all-cause mortality, disabling or non-disabling stroke, or hospitalisations for valve-related symptoms or worsening congestive heart failure (CHF). Early safety defined as all-cause mortality, stroke (disabling and non-disabling), life-threatening bleeding, acute kidney injury, coronary artery obstruction requiring intervention, major vascular complication, valve-related dysfunction requiring repeat procedure). Severe renal dysfunction defined as GFR ≤30 ml/min/m².

[1] 19 missing data (0 in transaxillary TAVR); **[2]** 76 missing data (59 in transaxillary TAVR); **[3]**16 missing data (1 in transaxillary TAVR); **[4]** 32 missing data (0 in transaxillary TAVR); [5] 169 missing data (2 in transaxillary TAVR; **[6]** 285 missing data (64 in transaxillary TAVR).

AR: aortic regurgitation; AVR: aortic valve replacement; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; SD: standard deviation; TAVR: transcatheter aortic valve replacement; TIA: transient ischaemic attack; TTE: transthoracic echocardiography