JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 74, NO. 22, 2019
© 2019 THE AUTHORS. PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION. THIS IS AN OPEN ACCESS ARTICLE UNDER THE CC BY-NC-ND LICENSE (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Femoral Versus Nonfemoral Peripheral Access for Transcatheter Aortic Valve Replacement

Sylvain Beurtheret, MD,[a] Nicole Karam, MD, PhD,[b,c,d] Noemie Resseguier, MD,[e] Remi Houel, MD,[a] Thomas Modine, MD, PhD,[f] Thierry Folliguet, MD, PhD,[g] Chekrallah Chamandi, MD,[b,c,d] Olivier Com, MD,[h] Richard Gelisse, MD,[h] Jacques Bille, MD,[h] Patrick Joly, MD,[h] Nicolas Barra, MD,[h] Alain Tavildari, MD,[h] Philippe Commeau, MD,[i] Sebastien Armero, MD,[j] Mathieu Pankert, MD,[k] Michel Pansieri, MD,[k] Sabrina Siame,[a] René Koning, MD,[l] Marc Laskar, MD, PhD,[m] Yvan Le Dolley, MD,[a] Arnaud Maudiere, MD,[a] Bertrand Villette, MD,[a] Patrick Khanoyan, MD,[h] Julien Seitz, MD,[h] Didier Blanchard, MD,[b,c,d] Christian Spaulding, MD, PhD,[b,c,d] Thierry Lefevre, MD,[n] Eric Van Belle, MD, PhD,[o] Martine Gilard, MD, PhD,[p] Helene Eltchaninoff, MD, PhD,[q] Bernard Iung, MD, PhD,[r] Jean Philippe Verhoye, MD, PhD,[s] Ramzi Abi-Akar, MD,[t] Paul Achouh, MD, PhD,[t] Thomas Cuisset, MD, PhD,[u] Pascal Leprince, MD, PhD,[v] Eloi Marijon, MD, PhD,[b,c,d] Hervé Le Breton, MD, PhD,[w] Antoine Lafont, MD, PhD[b,c,d]

ABSTRACT

BACKGROUND Femoral access is the gold standard for transcatheter aortic valve replacement (TAVR). Guidelines recommend reconsidering surgery when this access is not feasible. However, alternative peripheral accesses exist, although they have not been accurately compared with femoral access.

OBJECTIVES This study compared nonfemoral peripheral (n-FP) TAVR with femoral TAVR.

METHODS Using the data from the national prospective French registry (FRANCE TAVI [French Transcatheter Aortic Valve Implantation]), this study compared the characteristics and outcomes of TAVR procedures according to whether they were performed through a femoral or a n-FP access, using a pre-specified propensity score–based matching between groups. Subanalysis during 2 study periods (2013 to 2015 and 2016 to 2017) and among low/intermediate-low and intermediate-high/high volume centers were performed.

RESULTS Among 21,611 patients, 19,995 (92.5%) underwent femoral TAVR and 1,616 (7.5%) underwent n-FP TAVR (transcarotid, n = 914 or trans-subclavian, n = 702). Patients in the n-FP access group had more severe disease (mean logistic EuroSCORE 19.95 vs. 16.95; $p < 0.001$), with a higher rate of peripheral vascular disease, known coronary artery disease, chronic pulmonary disease, and renal failure. After matching, there was no difference in the rate of post-procedural death and complications according to access site, except for a 2-fold lower rate of major vascular complications (odds ratio: 0.45; 95% confidence interval: 0.21 to 0.93; $p = 0.032$) and unplanned vascular repairs (odds ratio: 0.41; 95% confidence interval: 0.29 to 0.59; $p < 0.001$) in those who underwent n-FP access. The comparison of outcomes provided similar results during the second study period and in intermediate-high/high volume centers.

CONCLUSIONS n-FP TAVR is associated with similar outcomes compared with femoral peripheral TAVR, except for a 2-fold lower rate of major vascular complications and unplanned vascular repairs. n-FP TAVR may be favored over surgery in patients who are deemed ineligible for femoral TAVR and may be a safe alternative when femoral access risk is considered too high. (J Am Coll Cardiol 2019;74:2728–39)
© 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the [a]Cardiac Surgery Department, Saint Joseph Hospital, Marseille France; [b]Paris Cardiovascular Research Center, INSERM Unit 970, Paris, France; [c]Université Paris Descartes, Sorbonne Paris Cité, Paris, France; [d]Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Cardiology Department, Paris, France; [e]Department of Biostatistics and Public Health, La Timone Hospital, Marseille, France; [f]Cardiac Surgery Department, Cardiologic University Hospital, Lille, France; [g]Department of Cardiothoracic Surgery and Transplantation, University of Lorraine, Centre Hospitalier Universitaire Brabois, Vandoeuvre les

ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2019.09.054

Since its introduction in 2002, transcatheter aortic valve replacement (TAVR) has expanded rapidly as an alternative to surgical aortic valve replacement in patients at high and intermediate procedural risk (1–4).

Femoral peripheral (FP) access is the most studied and widely used access for TAVR procedures; it allows exclusive percutaneous intervention (5). However, despite the improvement in device profiles and procedural techniques, FP access cannot be performed in approximately 10% to 15% of patients due to iliofemoral arteriopathy, tortuosity, severe calcifications, aortic aneurysm, mural thrombus, or previous vascular surgery (6). Current guidelines recommend that surgery be reconsidered in patients ineligible for FP access, mainly based on studies that assessed the safety of transapical access (1,7). However, alternative nonfemoral peripheral (n-FP) accesses were recently developed (8–11). No randomized trial has compared the outcome of TAVR according to the access site, and observational study–derived comparisons have been limited by the difference in patient characteristics between the groups, with patients with more severe disease undergoing n-FP TAVR. Although propensity-matched comparison of transthoracic and FP TAVR has shown higher rates of adverse periprocedural events and death with central or transthoracic access (e.g., transapical or transaortic) (12,13), no similar comparisons have been made between n-FP (transcarotid or trans-subclavian) and FP TAVR.

SEE PAGE 2740

Using data from the national prospective French registry, the FRANCE TAVI (French Transcatheter Aortic Valve Implantation) registry, we compared 30-day outcomes of TAVR procedures according to whether they were performed through FP or n-FP access. Outcomes were compared after propensity score–based matching of patients with FP and n-FP interventions, with an assessment of temporal evolution in practices and outcomes during 2 critical periods (i.e., 2013 to 2015 and 2016 to 2017) and among low/intermediate-low and intermediate-high/high volume centers.

ABBREVIATIONS AND ACRONYMS

FP = femoral peripheral
CI = confidence interval
n-FP = nonfemoral peripheral
OR = odds ratio
PM = pacemaker
TAVR = transcatheter aortic valve replacement

METHODS

FRANCE TAVI REGISTRY. The FRANCE TAVI registry was launched in January 2013, in continuity with the France 2 Registry, on the initiative of the Groupe Atherome coronaire et Cardiologie Interventionnelle, the Interventional Cardiology working group of the French Society of Cardiology, with the participation of the French Society of Thoracic and Cardiovascular Surgery. It was approved by the Institutional Review Board of the French Ministry of Higher Education and

Nancy, France; [h]Cardiology Department, Saint Joseph Hospital, Marseille, France; [i]Department of Cardiology, Clinique des Fleurs Ollioules, Ollioules, France; [j]Department of Cardiology, Hôpital Européen, Marseille, France; [k]Department of Cardiology, Centre Hospitalier Henri Duffaut, Avignon, France; [l]Cardiology Service, Saint Hilaire Clinic, Rouen, France; [m]Department of Cardiac Surgery, Centre Hospitalier Dupuytren, Limoges, France; [n]Paris South Cardio-vascular Institute, Jacques-Cartier Private Hospital, Massy, France; [o]Department of Cardiology, University of Lille 2, Regional University Hospital Centre of Lille, National Institute of Health and Medical Research U1011, University Hospital Federation Integra, Lille, France; [p]Department of Cardiology, La Cavale Blanche University Hospital Centre, Optimization of Physiological Regulations, Science and Technical Training And Research Unit, University of Western Brittany, Brest, France; [q]Cardiology Service, Rouen-Charles-Nicolle University Hospital Centre, National Institute of Health and Medical Research U644, Rouen, France; [r]Department of Cardiology, University Hospital Department Fire and Paris-Diderot University, Public Assistance Hospitals of Paris, Bichat Hospital, Paris, France; [s]Thoracic and Cardiovascular Surgery Service, Pontchaillou University Hospital Centre, University of Rennes 1, Signal and Image Treatment Laboratory (LTSI), National Institute of Health and Medical Research U1099, Rennes, France; [t]Cardiac Surgery Department, Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Cardiology Department, Paris, France; [u]Cardiology Department, La Timone Hospital, Marseille, France; [v]Cardiac Surgery Department, Sorbonne-Pierre-et-Marie-Curie University, Assistance Publique-Hôpitaux de Paris, Groupe Hospitalier de la Pitié Salpêtrière, Paris, France; and the [w]Cardiology and Vascular Diseases Service, Pontchaillou University Hospital Centre, Centre for Clinical Investigation 804, University of Rennes 1, Signal and Image Treatment Laboratory, National Institute of Health and Medical Research U1099, Rennes, France. Edwards Lifesciences and Medtronic partly funded the FRANCE TAVI registry. Dr. Karam has received consultant fees from Abbott. Dr. Modine has been a consultant for Abbott, Edwards Lifesciences, Medtronic, and Microport. Dr Commeau has received consultant fees from Edwards, Abbott, and Boston Scientific. Dr. Koning has clinical research relationships with Boehringer Ingelheim, Boston Scientific, Abbott, Biosensor, and Biotronik. Dr. Seitz is a shareholder in Volta Medical; and has received consulting fees from Biosense Webster and Abbott. Dr. Spaulding has been a consultant for Medtronic. Dr. Spaulding has received consulting fees from Abiomed, Zoll, Medtronic, and Medpass. Dr. Lefevre has served as a proctor for Edwards Lifesciences and Abbott. Dr. Eltchaninoff has served as a proctor for and received lecture fees from Edwards Lifesciences. Dr. Iung has been a consultant for Edwards Lifesciences; and has received speaker fees from Boehringer Ingelheim and Novartis. Dr. Leprince has served as a proctor for Medtronic and Edwards. Dr. Le Breton has received speaker fees from Edwards Lifesciences and Medtronic. Dr. Lafont has served as a proctor for Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received May 17, 2019; revised manuscript received September 12, 2019, accepted September 15, 2019.

Research and by the National Commission for Data Protection and Liberties, whose principles are in line with the General Data Protection Regulation. FRANCE TAVI is registered with ClinicalTrials.gov (Registry of Aortic Valve Bioprostheses Established by Catheter; NCT01777828).

Designed as an all-comers registry, the FRANCE TAVI registry prospectively includes all patients undergoing TAVR procedures for severe aortic valve stenosis in 50 active TAVR centers in France. The decision to perform TAVR and the choices of access site and prosthesis type are made by a multidisciplinary heart team in each participating center. Procedures and post-procedural management are performed in accordance with the routine protocol of each site. A 30-day follow-up is recommended in the case report form and is performed either on site or by telephone contact with the patient and the patient's physician according to the participating site preference. Patients included in the registry provide written informed consent for the procedure and for anonymous processing of their data.

Data collection. The FRANCE TAVI dataset is filled through a dedicated web-based interface from the French Society of Cardiology. Collected data include baseline, procedural, and outcome characteristics. The database is managed by the French Society of Cardiology, which implements regular data quality checks, including range checks and assessments of internal consistency. In cases of missing, extreme, or inconsistent values, centers are contacted and asked to verify and modify the records as appropriate.

Outcomes are site-reported and standard definitions are used to enter the data. Major complications, including valve migration or embolization, major vascular complications, and bleeding were defined according to Valve Academic Research Consortium 2 criteria (14,15). Accordingly, major bleeding was defined as overt bleeding either associated with a decrease in hemoglobin level of at least 3.0 g/dl or requiring transfusion of at least 2 U of whole blood or red blood cells, or bleeding that caused hospitalization or permanent injury, or required surgery. Unplanned vascular repair was defined as any vascular injury that led to unplanned surgery or stent implantation. Renal failure was defined as an at least 1.5 increase in serum creatinine level compared with baseline or an increase of >0.3 mg/dl (26.4 mmol/l).

Study population. Based on criteria specified by the French Ministry of Health, patients included in the registry were adults with severe aortic valve stenosis. Severe aortic valve stenosis was diagnosed as defined by international guidelines. All patients enrolled in the FRANCE TAVI registry between January 2, 2013 and December 31, 2017 were included in the study. Patients with missing data on valve type, access site, or propensity score variables (Online Table 1) were excluded from the analysis. The study flowchart is presented in **Figure 1**.

OPERATIVE TECHNIQUE. This was a multicentric observational study in which each center used its own technique. FP TAVR was percutaneous in most cases. It was a surgical approach in all cases of n-FP TAVR. The surgical cutdown of the trans-subclavian access (including transaxillary or distal subclavian) was performed through an infraclavicular incision respecting the brachial plexus. In case of a carotid approach, a 3- to 4-cm long, low cervical incision was performed to expose the sternocleidomastoid muscle. The jugular vein, the Vagus nerve, and the respiratory tract were identified. Theoretically, the left access for n-FP TAVR was often preferred over the right access because it provided superior coaxial alignment with the ascending aorta and optimal positioning of the prosthesis.

Conscious sedation with local anesthesia or general anesthesia was possible with all pathways.

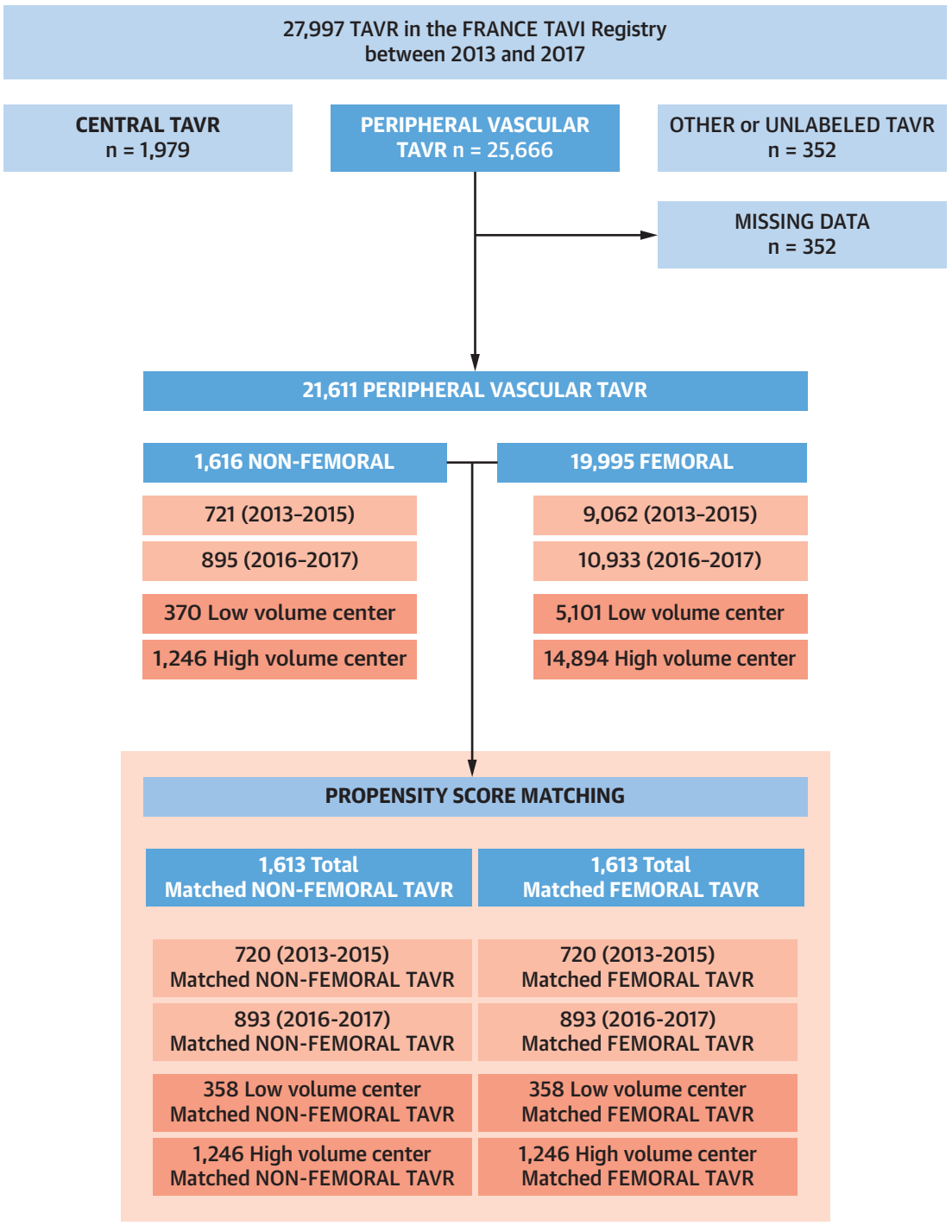
ENDPOINTS. The primary endpoint for the prespecified propensity score–matching based comparison was procedural mortality (either in-hospital mortality or 30-day mortality). Secondary endpoints included all other in-hospital complications (Online Table 2). Of note, 30-day follow-up was available in all patients.

STATISTICAL ANALYSIS. This report was prepared in compliance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for observational studies (16).

Baseline clinical characteristics were first described and compared between the 2 groups of interest (FP TAVR vs. n-FP TAVR). Quantitative variables were presented as mean ± SD (assumption of normal distribution was assessed graphically using histograms and QQ plots) and compared using Student's *t*-test. Categorical variables were presented as numbers (percentages) and compared using the chi-square test when appropriate (Fisher exact test otherwise).

Among patients with peripheral TAVR (n = 25,666), baseline characteristics differences were considered to be small because standardized differences were <0.2 (median standardized difference was 0.05) between those with a complete dataset (n = 21,611) versus those with ≥1 missing data (n = 4,055), which represented 14.5% of the overall population. We performed an unadjusted comparison between n-FP

FIGURE 1 Study Flowchart



Among 27,997 patients included in the FRANCE TAVI (French Transcatheter Aortic Valve Implantation) registry, 21,611 patients were included in the study. Patients who underwent nonfemoral peripheral (n-FP) transcatheter aortic valve replacement (TAVR) (n = 1,613) with complete data were matched with 1,613 patients who underwent FP TAVR for comparison purposes.

and FP approaches among patients with an incomplete record to account for missing data.

Propensity score–based matching was developed using a logistic regression model that included 18 preprocedural variables known to be related to outcomes and/or to the access site (regardless of their statistical significance, using a non-parsimonious approach) and the center volume to abolish a possible "center effect." The center volume was divided into 4 groups using quartiles: low volume (≤67 procedures per year); low-intermediate volume (between 68 and 104 procedures per year); intermediate-high volume (between 105 and 155 procedures per year); and high volume (≥156 procedures per year). This model allowed calculation of the probability (propensity score) of n-FP TAVR access for each patient. Using the propensity score, n-FP TAVR cases were matched to FP TAVR cases. A nearest-neighbor 1:1 matching algorithm on the basis of the propensity score was applied, with a caliper width of 0.2 SD of the logit of the propensity score. Standardized differences before and after matching were estimated (with their 95% confidence interval [CI]) to assess the quality of the propensity score matching procedure. A mirrored histogram of distribution of propensity scores for n-FP TAVR (bars below the zero line) versus FP TAVR (bars above the zero line) is presented in Online Figure 1.

Logistic regression models were used to estimate the odds ratio (OR) of each endpoint for n-FP TAVR access and adjusted for the type of prosthesis implanted and the study period. The implanted prosthesis type and the study period, which were post-baseline covariates, were therefore not included in the propensity score model and were taken into account as possible confounding factors in the multivariate regression model.

To further account for the evolution in catheter size, device performance, and practices during the study period, a first subanalysis was performed with a comparison of FP to n-FP TAVR in each study period separately using the same methodology. A second subanalysis was performed with a comparison of FP TAVR to n-FP TAVR in low/intermediate-low volume centers and intermediate-high/high volume centers separately using the same methodology. To ensure that the overall outcomes were not driven by one compared with the other n-FP approach, we performed an unadjusted comparison between transcarotid and trans-subclavian approaches.

All tests were 2-sided, and p values <0.05 were considered to be statistically significant. Statistical analyses were performed using R software version 3.4.1 (R Foundation, Vienna, Austria). The R package MatchIt was used for the propensity score–based matching.

RESULTS

During the study period, 27,997 patients were included in the FRANCE TAVI registry. Of those, 352 had missing data regarding the access site, 1,979 underwent a central access (transapical or transaortic), and 4,055 had at least 1 missing data among propensity score variables. Baselines characteristics and impact of access type on the outcome of the unmatched excluded population are presented in Online Tables 3 and 4. Therefore, 21,611 patients underwent peripheral vascular access and were included in the study.

CHARACTERISTICS OF THE POPULATION BEFORE MATCHING. FP access was used in 19,995 patients (92.5%), whereas n-FP access was used in 1,616 cases (7.5%). Baseline characteristics of the nonmatched population are presented in Online Table 5.

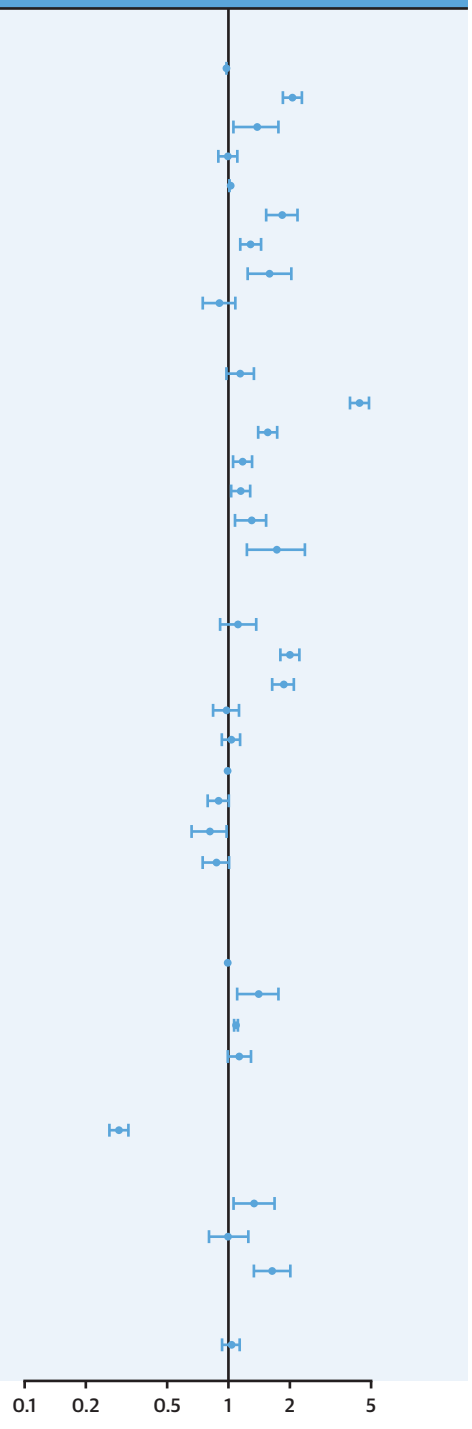
Patients in the n-FP access group were younger than those in the FP access group (81.83 years vs. 83.34 years; $p < 0.001$) and were more frequently men (64.60% vs. 47.13%; $p < 0.001$). Patients in the n-FP access group had more severe disease. Their mean logistic EuroSCORE was higher (19.95 vs. 16.99; $p < 0.001$), their ejection fractions were lower (54.45% vs. 56.48%; $p < 0.001$), with higher rates of known coronary artery disease (63.37% vs. 46.41%; $p < 0.001$), previous cardiac surgery (21.78% vs. 13.06%; $p < 0.001$), diabetes mellitus (28.71% vs. 25.64%; $p = 0.007$), renal failure (51.92% vs. 47.37%; $p < 0.001$), peripheral vascular disease (50.25% vs. 18.69%; $p < 0.001$), and chronic pulmonary disease (25.43% vs. 18.04%; $p < 0.001$).

Forest plots of patients' factors associated with n-FP TAVR versus factors associated with FP TAVR are presented in **Figure 2**.

CHARACTERISTICS OF THE MATCHED POPULATION. Baseline characteristics of the matched population according to access type ($n = 1,613$ in each group) are shown in **Table 1**. In the n-FP access group, mean age was 81.85 years versus 82.08 years in the FP group ($p = 0.382$), with 64.54% men versus 63.30% men ($p = 0.453$). A nonelective procedure was performed in 8.31% of cases versus 8.68% of cases ($p = 0.705$). Stroke history was present in 12.09% of cases versus 13.64% of cases ($p = 0.189$). Overall, patients' characteristics were similar for all variables included in the propensity score. Balloon expandable prostheses

FIGURE 2 Patients' Factors Associated With n-FP TAVR Versus FP TAVR

	OR	Lower CI	Upper CI
General Characteristics			
Age	0.97	0.97	0.98
Male	2.05	1.84	2.28
BMI (underweight)	1.38	1.06	1.76
BMI (overweight)	0.99	0.89	1.11
Logistic EuroSCORE	1.02	1.01	1.02
Indication (operative CI)	1.83	1.54	2.18
Indication (high surgical risk)	1.28	1.14	1.45
Indication (other)	1.59	1.24	2.03
Non-elective procedure	0.90	0.75	1.08
Extra Cardiac History			
Previous stroke/TIA	1.14	0.98	1.33
Peripheral vascular disease	4.39	3.96	4.87
Chronic pulmonary disease	1.55	1.38	1.74
Diabetes mellitus	1.17	1.04	1.31
Renal failure (moderate)	1.15	1.03	1.29
Renal failure (severe)	1.29	1.08	1.53
Renal failure (dialysis)	1.73	1.23	2.37
Cardiac History			
Cardiac symptoms	1.11	0.91	1.37
Coronary disease	2.00	1.80	2.22
Previous cardiac surgery	1.86	1.64	2.10
Previous permanent pacemaker	0.98	0.84	1.13
Previous SV arrhythmia	1.03	0.92	1.14
Ejection fraction	0.99	0.99	0.99
Pulmonary HT (moderate)	0.89	0.79	1.01
Pulmonary HT (severe)	0.81	0.66	0.98
Pulmonary HT (non-measurable or non-available)	0.87	0.75	1.01
Aortic Valve Characteristics			
Mean aortic gradient	0.99	0.99	0.99
Aortic valve area	1.40	1.1	1.75
Aortic annulus	1.09	1.07	1.11
Moderate or severe AR	1.13	0.99	1.29
Valve Type			
Balloon-expandable	0.29	0.26	0.32
Center Size			
Low-intermediate volume quartile	1.33	1.06	1.68
High-intermediate volume quartile	0.99	0.80	1.25
High volume quartile	1.63	1.33	2.01
Study Period			
2016-2017	1.03	0.93	1.14



Odds ratios (ORs) expressing the probability of having n-FP TAVR. AR = aortic regurgitation; BMI = body mass index; CI = confidence interval; HT = hypertension; SV = supraventricular; TIA = transient ischemic attack; other abbreviations as in Figure 1.

TABLE 1 Baseline Characteristics of the Total Matched Population According to the Access Type

	Nonfemoral Access (n = 1,613)	Femoral Access (n = 1,613)	p Value	Standardized Difference
General characteristics				
Age, yrs	81.85 ± 7.31	82.08 ± 7.57	0.382	0.03 (−0.04 to 0.10)
Male	1,041 (64.54)	1,021 (63.30)	0.463	0.03 (−0.04 to 0.09)
Body mass index, kg/m^2			0.935	0.01 (−0.06 to 0.08)
Normal	613 (38.00)	615 (38.13)		
Underweight	69 (4.28)	73 (4.53)		
Overweight	431 (57.72)	925 (57.35)		
Logistic EuroSCORE, %	19.94 ± 13.91	19.43 ± 13.81	0.310	0.04 (−0.03 to 0.11)
Main indication			0.445	0.06 (−0.01 to 0.13)
Operative contraindication	217 (13.45)	216 (13.39)		
High surgical risk	928 (57.53)	969 (60.07)		
Frailty	386 (23.93)	353 (21.88)		
Other	82 (5.08)	75 (4.65)		
Nonelective procedure	134 (8.31)	140 (8.68)	0.705	0.01 (−0.06 to 0.08)
Extracardiac history				
Previous stroke/TIA	195 (12.09)	220 (13.64)	0.189	0.05 (−0.02 to 0.11)
Peripheral vascular disease	809 (50.15)	804 (49.85)	0.860	0.01 (−0.06 to 0.07)
Chronic pulmonary disease	408 (25.29)	405 (25.11)	0.903	<0.01 (−0.06 to 0.07)
Diabetes mellitus	464 (28.77)	469 (29.08)	0.846	0.01 (−0.06 to 0.07)
Renal failure			0.896	0.02 (−0.04 to 0.09)
None	777 (48.17)	765 (47.43)		
Moderate	622 (38.56)	642 (39.80)		
Severe	172 (10.66)	164 (10.17)		
Dialysis	42 (2.60)	42 (2.60)		
Cardiac history				
Cardiac symptoms	1,507 (93.43)	1,499 (92.93)	0.576	0.02 (−0.05 to 0.09)
Coronary disease	1,021 (63.30)	1,006 (62.37)	0.585	0.02 (−0.05 to 0.09)
Previous cardiac surgery	352 (21.82)	356 (22.07)	0.865	0.01 (−0.06 to 0.07)
Previous permanent pacemaker	212 (13.14)	237 (14.69)	0.204	0.04 (−0.02 to 0.11)
Previous SV arrhythmia	579 (35.90)	589 (36.52)	0.714	0.01 (−0.05 to 0.08)
Ejection fraction	54.46 ± 13.26	54.31 ± 13.43	0.754	0.01 (−0.06 to 0.08)
Pulmonary hypertension			0.727	0.04 (−0.03 to 0.11)
None	480 (29.76)	492 (30.50)		
Moderate	700 (43.40)	702 (43.52)		
Severe	135 (8.37)	118 (7.32)		
Nonmeasurable or NA	298 (18.47)	301 (18.66)		
Aortic valve characteristics				
Mean aortic gradient, mm Hg	46.29 ± 14.40	46.02 ± 14.35	0.593	0.02 (−0.05 to 0.09)
Aortic valve area, cm^2	0.71 ± 0.23	0.72 ± 0.21	0.568	0.02 (−0.05 to 0.09)
Aortic annulus, mm	24.54 ± 2.68	24.31 ± 2.69	0.019	0.08 (0.01 to 0.16)
Moderate or severe AR	301 (22.40)	281 (20.81)	0.319	0.04 (−0.04 to 0.11)
Prosthesis type			<0.001	0.65 (0.58 to 0.72)
Self-expanding prosthesis	1074 (66.58)	574 (35.59)		
Balloon-expandable prosthesis	539 (33.42)	1,039 (64.41)		
Center volume			0.998	0.01 (−0.06 to 0.07)
Low volume quartile	108 (6.70)	107 (6.63)		
Low-intermediate volume quartile	262 (16.24)	262 (16.24)		
High-intermediate volume quartile	327 (20.27)	331 (20.52)		
High volume quartile	916 (56.79)	913 (56.60)		
Time period			0.229	0.04 (−0.03 to 0.11)
2013–2015	719 (44.58)	753 (46.68)		
2016–2017	894 (55.42)	860 (53.32)		

Values are mean ± SD and n (%).

AR = aortic regurgitation; NA = not available; SV = supraventricular; TIA = transient ischemia attack.

were the most frequent prostheses used in the FP access group (64.41%), whereas self-expandable prostheses were the most frequently used in the n-FP access group (66.58%). Among the n-FP access group, 911 (56.5%) patients underwent transcarotid access and 702 (43.5%) patients underwent trans-subclavian access.

IMPACT OF ACCESS SITE ON THE OUTCOME. Impact of access type on outcomes in the unmatched population is presented in Online Table 6. There were more strokes (OR: 1.65; 95% CI: 1.22 to 2.20; p = 0.002), acute renal failures (OR: 1.39; 95% CI: 1.05 to 1.81; p = 0.024), and major bleedings (OR: 1.22; 95% CI: 1.01 to 1.47; p = 0.040), but less annulus ruptures (OR: 0.12; 95% CI: 0.00 to 0.84; p = 0.027), major vascular complications (OR: 0.55; 95% CI: 0.28 to 0.95; p = 0.031), and unplanned vascular repairs (OR: 0.45; 95% CI: 0.33 to 0.59; p < 0.001) in the n-FP group.

Among the 1,613 matched n-FP cases, mean post-procedural length of stay was significantly higher in the n-FP group (8.86 days vs. 7.98 days; p = 0.006). The procedural mortality rate was 3.97% versus 2.91% in the FP group (p = 0.211); the ST-segment elevation myocardial infarction rate was 0.25% versus 0.19% (p = 0.774), the stroke rate was 3.35% versus 2.17% (p = 0.156), the major vascular complications rate was 0.68% versus 1.36% (p = 0.032), and unplanned vascular repairs occurred in 3.10% of cases versus 6.70% of cases (p < 0.001). Compared with FP access, n-FP access was not associated with increased procedural mortality (OR: 1.29; 95% CI: 0.87 to 1.94; p = 0.211) or associated with an increased risk of stroke (OR: 1.38; 95% CI: 0.88 to 2.19; p = 0.156). As shown in **Table 2**, there was no difference in the rate of any complications according to the access site in the matched population, except for a 2-fold lower rate of major vascular complications (OR: 0.45; 95% CI: 0.21 to 0.93; p = 0.032) and unplanned vascular repairs (OR: 0.41; 95% CI: 0.29 to 0.59; p < 0.001) in the n-FP access group. In multivariate logistic regression, FP access was an independent predictor of major vascular complications (Online Table 7).

In the n-FP group, unmatched comparison between the transcarotid and trans-subclavian accesses (Online Tables 8 and 9) showed no difference in the stroke rate (3.62% and 2.99%, respectively; p = 0.485). There were more renal failures (OR: 1.78; 95% CI: 1.03 to 3.16; p = 0039) and major bleedings (OR: 1.82; 95% CI: 1.25 to 2.68; p = 0.002) but less hemorrhagic shocks (OR: 0.26; 95% CI: 0.06 to 0.91; p = 0.035) and major vascular complications (OR: 0.21; 0.04 to 0.80; p = 0.021).

TABLE 2 Impact of Access Type on Outcome of the Matched Population

	Nonfemoral Access (n = 1,613)	Femoral Access (n = 1,613)	Multivariate Analysis	
			OR* (95% CI)	p Value
Procedural mortality	64 (3.97)	47 (2.91)	1.29 (0.87–1.94)	0.211
STEMI	4 (0.25)	3 (0.19)	0.81 (0.19–3.87)	0.774
Stroke	54 (3.35)	35 (2.17)	1.38 (0.88–2.19)	0.156
Annulus rupture	0 (0.00)	3 (0.19)	0.14 (0.00–1.62)	0.126
Aortic dissection	4 (0.25)	2 (0.12)	1.63 (0.32–10.45)	0.564
Valve migration/embolization	16 (0.99)	11 (0.68)	1.09 (0.50–2.48)	0.833
Tamponade	24 (1.49)	18 (1.12)	1.38 (0.73–2.65)	0.321
Permanent pacemaker insertion	287 (17.79)	254 (15.75)	0.95 (0.78–1.16)	0.607
Pulmonary embolism	4 (0.25)	3 (0.19)	1.17 (0.27–5.57)	0.829
Renal failure	62 (3.84)	45 (2.79)	1.39 (0.92–2.11)	0.119
Renal dialysis	10 (0.62)	5 (0.31)	1.60 (0.54–5.34)	0.408
Major bleeding	138 (8.56)	121 (7.50)	1.06 (0.81–1.39)	0.676
Hemorrhagic shock	11 (0.68)	11 (0.68)	0.89 (0.37–2.14)	0.795
Unplanned vascular repairs	50 (3.10)	108 (6.70)	0.41 (0.29–0.59)	<0.001
Major vascular complications	11 (0.68)	22 (1.36)	0.45 (0.21–0.93)	0.032
Surgery under bypass	3 (0.19)	6 (0.37)	0.41 (0.09–1.52)	0.183
Infectious complication	72 (4.46)	67 (4.15)	0.97 (0.68–1.39)	0.861

Values are n (%) unless otherwise indicated. *Odds ratio (OR) expressing the excess of risk of complication for nonfemoral peripheral transcatheter aortic valve replacement after adjustment for prosthesis type and time period.

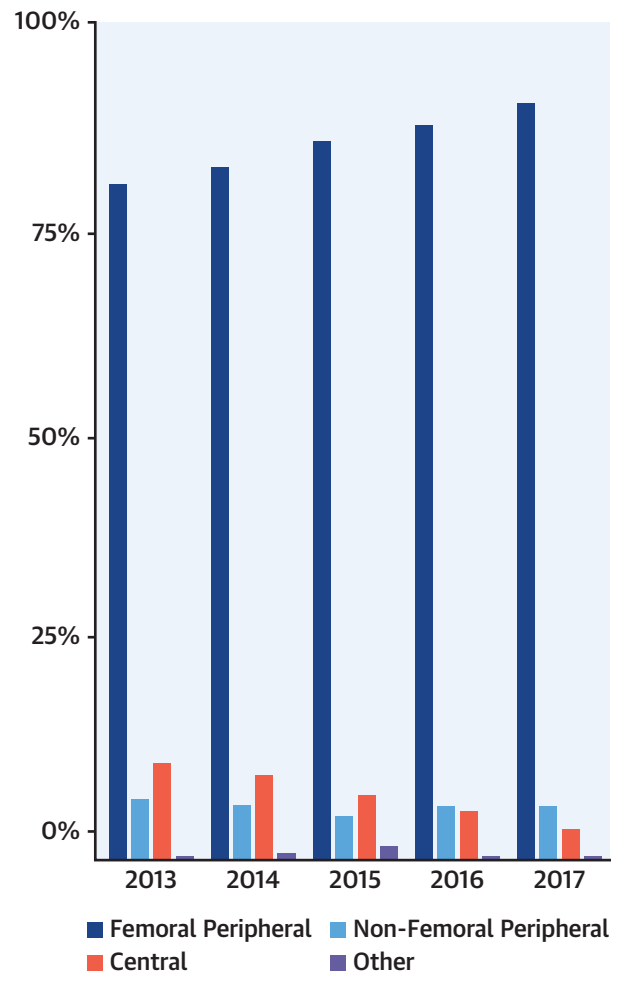
CI = confidence interval; STEMI = ST-segment elevation myocardial infarction.

Per-period subanalysis. Over the 5-year study period, the distribution of TAVR accesses significantly evolved (p < 0.001). The rate of FP TAVR increased from 79.95% in 2013 to 2015 to 89.12% in 2016 to 2017, with a massive decrease in central TAVR (i.e., transapical and transaortic) from 11.99% to 3.76%, whereas the rate of n-FP TAVR remained stable from 7.66% to 6.62% (**Figure 3**). Distribution of prostheses types across the 2 study periods are shown in Online Table 10.

In the total population (n = 21,611), mean post-procedural length of stay decreased in both groups (9.99 to 7.96 days in the n-FP group; p < 0.001; and 8.71 to 6.80 days in the FP group; p < 0.001). The procedural mortality rate decreased from 3.76% to 2.36% (p < 0.001), and the major vascular complications rate decreased significantly in the total population from 1.44% to 1.02% (p = 0.005). There was a nonsignificant decrease in stroke rate in the total population from 2.06% to 1.81% (p = 0.173).

When considering the 2016 to 2017 period separately, there was no difference in the rate of any complications according to the access site in the matched population, except for a 4-fold lower rate of major vascular complications (OR: 0.26; 95% CI: 0.07 to 0.78; p = 0.015) and a 2-fold lower rate of unplanned vascular repairs (OR: 0.47; 95% CI: 0.28 to 0.77; p = 0.002) in the n-FP access group. The

FIGURE 3 Evolution of the Distribution of Different Accesses for TAVR From 2012 to 2017



Among the 27,997 TAVR recipients included in the FRANCE-TAVI Registry between January 2013 and December 2017: femoral peripheral refers to transfemoral TAVR, nonfemoral peripheral includes trans-subclavian and transcarotid TAVR, central includes transapical and trans aortic TAVR, and other represent all the accesses not mentioned or not labeled. Abbreviations as in Figure 1.

complete per-period subanalysis is shown in Online Table 11.

Per-center volume subanalysis. In high-intermediate/high volume centers, there was no difference in the rate of complications according to the access site in the matched population, except for a 3-fold lower rate of major vascular complications (OR: 0.35; 0.13 to 0.84; $p = 0.018$) and a 2-fold lower rate of unplanned vascular repairs (OR: 0.44; 95% CI: 0.29 to 0.66; $p < 0.001$) in the n-FP access group. The per-center volume subanalysis is shown in Online Table 12.

DISCUSSION

In this large multicentric study that included all peripheral vascular TAVRs performed in France between 2013 and 2017, after a pre-specified propensity-based matching, the complications rate was low and similar between n-FP and FP TAVR, except for a 2-fold lower rate of major vascular complications or unplanned vascular repairs in the n-FP TAVR group (Central Illustration). The results were consistent over the 2 study periods, despite a reduction in procedural mortality, stroke, major vascular complications, and unplanned vascular repairs rates. The comparisons of outcomes provided similar results in intermediate-high/high volume centers.

TAVR has widely developed during the last several years, shifting from a technique that was solely used in patients who were ineligible for surgery, to a procedure that can now be considered in a large subset of patients, including those at lower risk. More recent studies have shown similar or even lower rates of death, stroke, or rehospitalization, compared with surgery, including among patients at low surgical risk (17,18). FP access is the current gold standard for TAVR procedures and is the first-line access site considered when TAVR is envisaged. Current guidelines state the feasibility of FP access is one of the key features that need to be assessed before choosing between TAVR and surgical valve replacement (1,7). However, despite great improvement in TAVR techniques and device profiles, approximately 10% to 15% of patients are still denied FP access due to unfavorable anatomy (6). In cases of intermediate-risk patients, European guidelines recommend that a surgical option be reconsidered (1). However, n-FP accesses have emerged as alternatives to FP, although no dedicated devices have been made for n-FP access (8,9,18). Those n-FP accesses have not been accurately compared with surgery or FP TAVR.

From an organizational point of view, n-FP TAVR is more invasive and more demanding than FP TAVR, in which procedural duration has decreased with time and general anesthesia can now be avoided in experienced centers (19). This led to the development of minimalistic TAVR with a shorter length of hospital stay and a simplification of procedure organization (20). Regarding safety and outcome, comparison of access types in observational studies has been limited by the great variability among patients who undergo different accesses, with patients with more severe disease undergoing n-FP TAVR. In our study, we performed propensity-based matching to allow an

CENTRAL ILLUSTRATION **Femoral or Nonfemoral Peripheral TAVR**

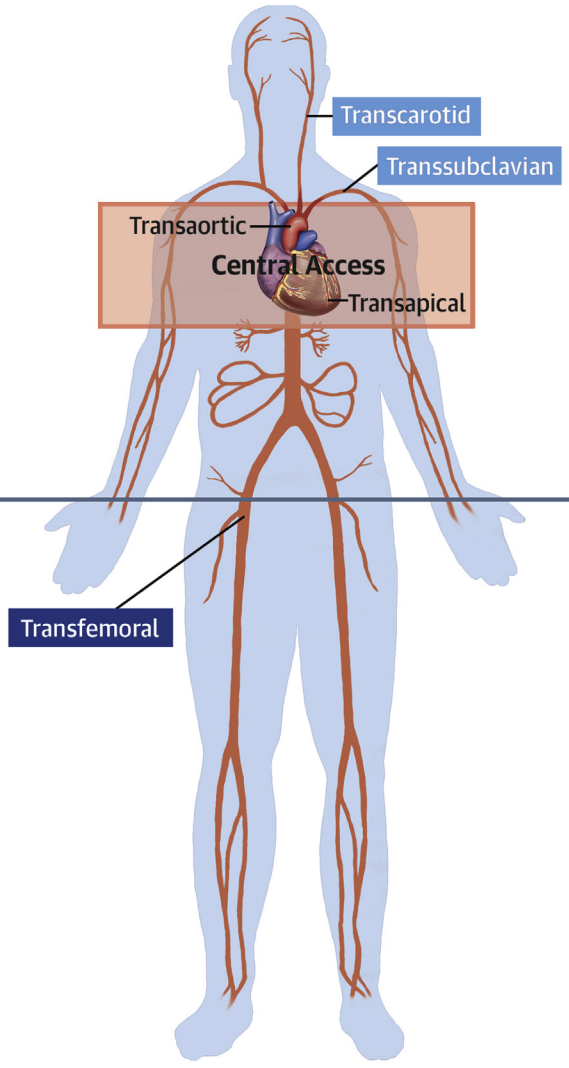
Non-Femoral Peripheral Vascular Access N = 1,616

Mean Logistic EuroSCORE I = 19.95%

Complications	n (%)
Operative mortality	64 (3.96)
Stroke	54 (3.34)
Unplanned vascular repair	51 (3.16)

Impact of Access Type on Outcome of the Matched Population

	OR* (95% CI)	P Value
Operative mortality	1.29 (0.87-1.94)	0.21
STEMI	0.81 (0.19-3.87)	0.77
Stroke	1.38 (0.88-2.19)	0.16
Annulus rupture	0.14 (0.00-1.62)	0.13
Aortic dissection	1.63 (0.32-10.45)	1.63
Tamponade	1.38 (0.73-2.65)	0.32
PM insertion	0.95 (0.78-1.16)	0.61
Renal failure	1.39 (0.92-2.11)	0.12
Major bleeding	1.06 (0.81-1.39)	0.68
Unplanned vascular repair	**0.41 (0.29-0.59)**	**<0.001**
Major vascular complications	**0.45 (0.21-0.93)**	**0.03**
Surgery under bypass	0.41 (0.09-1.52)	0.18



Complications	n (%)
Operative mortality	583 (2.92)
Stroke	362 (1.81)
Unplanned vascular repair	1,288 (6.44)

Femoral Peripheral Vascular Access N = 19,995

Mean Logistic EuroSCORE I = 16.99%

Beurtheret, S. et al. J Am Coll Cardiol. 2019;74(22):2728-39.

Comparison of patients from the FRANCE TAVI (French Transcatheter Aortic Valve Implantation) registry (2013 to 2017) who underwent transcatheter aortic valve replacement (TAVR), either through a femoral peripheral or a nonfemoral peripheral (n-FP) access. After propensity score–based matching, both groups had similar results. **Bold** indicates significant difference between the 2 groups. *Odds ratio (OR) expressing the excess of risk of complication for n-FP TAVR, after adjustment on prosthesis type and time period. PM = pacemaker; STEMI = ST-segment elevation myocardial infarction.

accurate comparison between groups. We did not observe any difference in procedural mortality or complication rates between FP and n-FP access, but n-FP access was associated with a lower rate of major vascular complications and unplanned vascular repairs compared with FP access. This confirmed the findings of previous studies (21,22).

The absence of increased risk of disabling stroke in n-FP TAVR was another major finding in our study. Despite all the advances in TAVR techniques, stroke remained the most feared complication, with evidence of silent and apparent microembolism in 50% to 94% of patients within the first month after TAVR (22,23). Cerebrovascular events were mainly attributed to the dislodgment of calcified debris and/or aortic valve tissue during the TAVR procedure (24). This hypothesis was further supported by the reduction of cerebral lesion volumes in diffusion-weighted magnetic resonance imaging in patients who underwent TAVR with embolic protection devices (25). In the case of n-FP access (mainly transcarotid), a specific mechanism for cerebrovascular events could be imagined, related to local complications and to the transient reduction in cerebral blood flow during the procedure. This theoretical increase in stroke rate was not observed in our study, which further supported a wider use of this access when FP access was deemed not feasible during the preoperative workup.

Improvements in device performance and operator experience led to a decrease in length of stay after the procedure and a reduction in the rates of death, stroke, major vascular complications, and unplanned vascular repairs. However, comparison between FP and n-FP access provided similar results in both study periods, regardless of volume center size. In particular, n-FP access remained associated with a lower rate of unplanned vascular repairs and a lower rate of major vascular complications, which highlighted the necessity of considering n-FP access in complex FP cases. Further studies and specific scores are needed to identify the patients at higher risk for major vascular complications or unplanned vascular repairs who would benefit from this alternative access.

STUDY LIMITATIONS. Despite the large number of patients included and the involvement of several centers in the study, several limitations have to be acknowledged. First, although propensity matching was performed to reduce indication bias, which allowed a more reliable comparison of patients according to the access site, the results had to be analyzed with caution because of the nonrandomized nature of the study. Some differences persisted between the groups. In particular, the most frequent prosthesis type differed according to the access site because we chose to match on only the baseline characteristics of the patients. However, the prosthesis type was adjusted in the multivariate regression model and was not likely to influence the results. Second, for the sake of matching, we excluded patients with incomplete data. However, unadjusted comparison between n-FP and FP approaches among excluded patients with incomplete data showed similar results, indicating that this did not introduce any bias. Third, only symptomatic strokes were reported, and there was no systematic cerebral imaging. Therefore, the rate of silent cerebrovascular embolisms was not assessed. However, the impact of these silent microembolisms remains to be determined.

CONCLUSIONS

Among peripheral vascular TAVR, after a prespecified, propensity-based matching, n-FP and FP TAVR provided similar results and a similar safety profile, except for a 2-fold lower rate of major vascular complications or unplanned vascular repairs in the n-FP TAVR group. Although FP access remains the first choice in TAVR, n-FP TAVR may be a safe alternative when femoral access risk is considered too high and may be favored over surgery in patients who are deemed ineligible for FP TAVR.

ADDRESS FOR CORRESPONDENCE: Dr. Sylvain Beurtheret, Saint Joseph Hospital, Cardiac Surgery Department, 26 bd de Louvain, 13008 Marseille, France. E-mail: sbeurtheret@hopital-saint-joseph.fr. Twitter: @Beurtheretsylv1, @nickaram, @EloiMarijon.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: n-FP arterial access for TAVR is associated with a lower risk of major vascular complications than femoral access and otherwise similar procedural outcomes.

TRANSLATIONAL OUTLOOK: The outcomes of patients with aortic stenosis who undergo TAVR with nonfemoral peripheral access should be compared with those managed with surgical aortic valve replacement.

REFERENCES

1. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739–91.

2. Mack MJ, Leon MB, Smith CR, et al. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015; 385:2477–84.

3. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet 2016;387:2218–25.

4. Ludman PF, Moat N, de Belder MA, et al. Transcatheter aortic valve implantation in the United Kingdom: temporal trends, predictors of outcome, and 6-year follow-up: a report from the UK Transcatheter Aortic Valve Implantation (TAVI) Registry, 2007 to 2012. Circulation 2015;131: 1181–90.

5. Auffret V, Lefevre T, Van Belle E, et al. Temporal trends in transcatheter aortic valve replacement in France: FRANCE 2 to FRANCE TAVI. J Am Coll Cardiol 2017;70:42–55.

6. Patel JS, Krishnaswamy A, Svensson LG, Tuzcu EM, Mick S, Kapadia SR. Access options for transcatheter aortic valve replacement in patients with unfavorable aortoiliofemoral anatomy. Curr Cardiol Rep 2016;18:110.

7. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;70:252–89.

8. Folliguet T, Laurent N, Bertram M, et al. Transcarotid transcatheter aortic valve implantation: multicentre experience in France. Eur J Cardiothorac Surg 2018;53:157–61.

9. Amat-Santos IJ, Rojas P, Gutiérrez H, et al. Transubclavian approach: a competitive access for transcatheter aortic valve implantation as compared to transfemoral. Catheter Cardiovasc Interv 2018;92:935–44.

10. Modine T, Sudre A, Delhaye C, et al. Transcutaneous aortic valve implantation using the left carotid access: feasibility and early clinical outcomes. Ann Thorac Surg 2012;93:1489–94.

11. Modine T, Lemesle G, Azzaoui R, Sudre A. Aortic valve implantation with the CoreValve ReValving System via left carotid artery access: first case report. J Thorac Cardiovasc Surg 2010; 140:928–9.

12. Blackstone EH, Suri RM, Rajeswaran J, et al. Propensity-matched comparisons of clinical outcomes after transapical or transfemoral transcatheter aortic valve replacement: a placement of aortic transcatheter valves (PARTNER)-I trial substudy. Circulation 2015;131:1989–2000.

13. Chollet T, Marcheix B, Boudou N, et al. Propensity-matched comparison of clinical outcomes after transaortic versus transfemoral aortic valve replacement. EuroIntervention 2018;14:750–7.

14. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. Eur Heart J 2012;33:2403–18.

15. Erlebach M, Head SJ, Mylotte D, et al. VARC endpoint definition compliance rates in contemporary transcatheter aortic valve implantation studies. EuroIntervention 2016;12:375–80.

16. Vandenbroucke JP. The making of STROBE. Epidemiology 2007;18:797–9.

17. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med 2019;380:1706–15.

18. Chamandi C, Abi-Akar R, Rodés-Cabau J, et al. Transcarotid compared with other alternative access routes for transcatheter aortic valve replacement. Circ Cardiovasc Interv 2018;11: e006388.

19. Husser O, Fujita B, Hengstenberg C, et al. Conscious sedation versus general anesthesia in transcatheter aortic valve replacement: the German Aortic Valve Registry. J Am Coll Cardiol Intv 2018;11:567–78.

20. Droppa M, Borst O, Katzenberger T, et al. Comparison of safety and periprocedural complications of transfemoral aortic valve replacement in local anesthesia in minimalist versus complete heart team. EuroIntervention 2019;14:e1819–25.

21. Généreux P, Webb JG, Svensson LG, et al. Vascular complications after transcatheter aortic valve replacement: insights from the PARTNER (Placement of AoRTic TraNscathetER Valve) trial. J Am Coll Cardiol 2012;60:1043–52.

22. Rodés-Cabau J, Dumont E, Boone RH, et al. Cerebral embolism following transcatheter aortic valve implantation: comparison of transfemoral and transapical approaches. J Am Coll Cardiol 2011;57:18–28.

23. Pagnesi M, Martino EA, Chiarito M, et al. Silent cerebral injury after transcatheter aortic valve implantation and the preventive role of embolic protection devices: a systematic review and meta-analysis. Int J Cardiol 2016;221:97–106.

24. Jochheim D, Zadrozny M, Ricard I, et al. Predictors of cerebrovascular events at mid-term after transcatheter aortic valve implantation - results from EVERY-TAVI registry. Int J Cardiol 2017;244:106–11.

25. Lansky AJ, Schofer J, Tchetche D, et al. A prospective randomized evaluation of the TriGuard™ HDH embolic DEFLECTion device during transcatheter aortic valve implantation: results from the DEFLECT III trial. Eur Heart J 2015;36: 2070–8.

KEY WORDS access site, outcome, TAVR

APPENDIX For supplemental tables and a figure, please see the online version of this paper.