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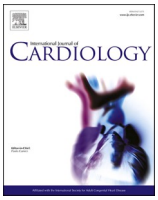

Transaxillary versus transfemoral access as default access in TAVI: A propensity matched analysis

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ABSTRACT

Background: Transfemoral (TF) access is default in transcatheter aortic valve implantation (TAVI). Transaxillary (TAx) access has been shown to be a safe alternative in case of prohibitive iliofemoral anatomy, but whether TAx as preferred access has similar safety and efficacy as TF access is unknown. The aim of this study was to compare outcomes between patients treated with self-expanding devices using TF or TAx route as preferred access in TAVI.

Methods: A single center cohort of 354 patients treated using TAx as preferred access and a multi-center cohort of 5980 patients treated using TF access were compared. Propensity score matching was used to reduce selection bias and potential confounding. After propensity score matching, each group consisted of 322 patients. Clinical outcomes according to VARC-2 were compared using chi-square test.

Results: In 6334 patients undergoing TAVI, mean age was 81.4 ± 7.0 years, 57% was female and median logistic EuroSCORE was 14.7% (IQR 9.5–22.6). In the matched population (age 79.3 ± 7.0, 50% female, logistic

Abbreviations: TAVI, transcatheter aortic valve implantation; TF, transfemoral; TAx, transaxillary; LIMA, left internal mammary artery; LAD, left anterior descending.

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EuroSCORE 13.4%, IQR 9.0–21.5), primary outcomes 30-day and one-year all-cause mortality were similar between Tax and TF groups (30 days: 5% versus 6%, $p = 0.90$; 1 year: 20% versus 16%, $p = 0.17$). Myocardial infarction was more frequent in patients undergoing Tax TAVI compared with TF (4% versus 1%, $p = 0.05$), but new permanent pacemakers were less frequently implanted (12% versus 21%, $p = 0.001$).
Conclusion: TAx as preferred access is feasible and safe with outcomes that are comparable to TF access.

1. Introduction

In recent guidelines by the European Society of Cardiology (ESC), transcatheter aortic valve implantation (TAVI) has become first line treatment in patients over 75 years of age with severe symptomatic aortic valve stenosis if transfemoral (TF) access is feasible [1]. Also, the 2020 American guidelines for valvular heart disease recommend shared decision making between SAVR and TAVI in patients with symptomatic severe aortic valve stenosis aged 65–80 years when TF TAVI is feasible [2]. In patients not suitable for transfemoral TAVI, the Heart team must consider surgical aortic valve replacement or TAVI using alternative trans-axillary (TAx), trans-carotid, transthoracic (trans apical or direct aortic) or transcaval access.

Currently, because of peripheral arterial disease, 5% to 6% of patients are deemed ineligible for TF TAVI [3,4]. The axillary artery is a safe alternative for the common femoral artery in patients when peripheral artery disease precludes TF access [5,6]. TAx access outperforms transapical and direct aortic approaches with respect to 30 day and in-hospital all-cause mortality both in a report from the TVT registry from 2019 and in a meta-analysis from the same year [7,8] and is the most common alternative TAVI access reported by the STS-ACC TVT registry [9]. TAx procedures are performed either using surgical cutdown under general anesthesia or a full percutaneous approach under local anesthesia with mild sedation [10,11]. TAx approach might become an adequate alternative in patients when TF access is less attractive, but not impossible, because of calcification, tortuosity or abdominal aneurysm without compromising procedure time or complexity. However, it is not known whether TAx access imposes increased risk of adverse outcomes after TAVI compared to TF approach when TF approach is not contra-indicated.

Currently, no trials have been conducted randomizing TF and TAx access when both are feasible. Recent propensity matched analysis and meta-analyses comparing TF with TAx access included TAx TAVI patients that were not eligible for TF TAVI [12–14]. Therefore, it is not known whether safety and efficacy of TAx access are comparable to the TF access when both are possible. We previously described the results of a unique cohort of patients in which TAx was the preferred TAVI access site, irrespective of the accessibility of TF access [15]. This TAx cohort allows for a better comparison with TF access than previously described TAx cohorts. The purpose of the present study was to compare safety and efficacy of the TAx route in this population in a propensity matched analysis against a very large cohort of patients with TAVI via TF access.

2. Methods

2.1. Study design and population

Data from the TAx cohort were collected from a single center registry of 485 consecutive patients who underwent TAVI using either the Medtronic CoreValve or EvolutR devices (Medtronic Inc., Minneapolis, Minnesota) between 2009 and 2016 in the Radboud University Medical Center (Nijmegen, the Netherlands). In this high-volume tertiary TAVI center, TAx was the default access irrespective of iliofemoral anatomy until early 2016, when TF access became preferred for reasons of efficiency and patient comfort. Of these 485 patients, 72 were excluded because of non-TAx access, 51 because they received another TAVI device and 8 because of either pure aortic regurgition or degenerated bioprosthesis as TAVI indication (Supplemental Fig. 1). A total of 362 consecutive patients with severe symptomatic aortic valve stenosis treated with TAx TAVI were included in this analysis.

All patients in this cohort underwent either conventional angiography or CT-reconstruction to assess axillary eligibility. All patients were treated under general anesthesia and surgical cutdown was used in all patients to gain access to the axillary artery, as described previously [15]. Data from TF TAVI patients were collected from a large multicenter registry of 12,381 patients with severe symptomatic aortic valve stenosis treated with TF TAVI using transfemoral access as default approach [16]. All patients were treated between 2007 and 2018. Valve in valve TAVI patients and those treated with balloon-expandable valves were excluded from this analysis, resulting in a patient population of $n = 354$ TAx and $n = 5980$ TF TAVI patients. Ethical approval was acquired by the ethics committee of each participating center. All TF TAVI patients provided written informed consent according to local policies of each center. All TAx patients provided informed consent for the procedure. Data were collected as part of an observational study, for which additional written informed consent was deemed not necessary by the institution's Ethics Committee because of the observational design of the study. Analysis of the data was approved by the institution's Ethics Committee.

2.2. Study procedures

Treatment indication and choice of valve type were assessed by the local heart team of each center. TAx TAVI procedures were performed between 2009 and 2016 in a single center through left axillary access This cohort was described in detail previously [15]. In hospital outcomes were collected at discharge. Longer term mortality data were requested at the Central Bureau for Statistics (The Hague, the Netherlands).

The transfemoral cohort was previously described as the CENTER study [16] and registered at ClinicalTrials.gov (NCT03588247). This collaboration of ten studies includes patients originally included between 2007 and 2018 in three national registries, two multicenter registries, four single center registries and one randomized controlled trial of patients residing in Israel, Brazil, France, Italy, Spain and the United States of America. All collaborating centers provided a dedicated database with baseline patient characteristics, echocardiographic data, procedural information, and long-term follow-up data. Transfemoral TAVI procedures were performed with both self-expandable valves and balloon-expandable valves (Edwards Lifesciences Inc., Irvine, California). For this analysis, only $n = 5890$ patients from the CENTER study undergoing TAVI with self-expandable valves were included. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

2.3. Clinical outcomes

We compared outcomes of patients undergoing TAx versus TF TAVI. Primary outcomes were 30-day and one-year all-cause mortality. Secondary outcomes included the following in hospital outcomes: emergent conversion to surgery, device success, stroke, transient ischemic attack (TIA), life-threatening and major bleeding, myocardial infarction, and permanent pacemaker implantation. All outcomes were defined according to the Second Valve Academic Research Consortium (VARC2). Device success was defined as a composite outcome of “absence of procedural mortality, correct positioning of a single valve, and intended

performance of the prosthetic heart valve" [17].

2.4. Statistical analysis

We compared clinical outcomes according to TAVI access using propensity score matching. In the overall unmatched population, baseline characteristics were tested for normal distribution. Accordingly, continuous variables were reported as mean with standard deviation or median with interquartile ratio (IQR). Differences between both cohorts were assessed with independent *t*-test or Mann Whitney *U* test. Categorical variables were presented as numbers and frequencies, and differences between groups were tested using chi-square test.

Secondly, propensity score matching was applied to minimize confounding and treatment selection bias by creating two well balanced patient groups. Baseline characteristics were tested in a univariate logistic regression model as predictors for TAVI access or for 30-day mortality. Predictors ($p < 0.1$) for either treatment (transfemoral or trans-axillary TAVI) or primary outcome (30-day mortality) were used to calculate the propensity score in a multivariate logistic regression model. As a result, the propensity score model included: age, gender, body mass index, history of myocardial infarction, history of percutaneous coronary intervention, history of coronary artery bypass graft, atrial fibrillation, history of stroke or transient ischemic attack, peripheral vascular disease, glomerular filtration rate < 30 ml/min/1.73m^2, aortic valve area, mean aortic valve gradient, peak aortic valve gradient, logistic EuroSCORE and year of TAVI procedure. Each patient treated with trans-axillary approach was matched with a patient treated with transfemoral approach. Matching was performed based on the propensity score using the one-to-one nearest neighbor method with no replacement and a caliper of 0.2 standard deviation of the logit of the propensity score. Supplemental Fig. 1 displays the distribution of the propensity score across the matched and unmatched population. Both in the unmatched and the propensity matched population, primary and secondary outcomes were compared between groups using chi-square test. All statistical tests were two-tailed, and a *P*-value of <0.05 was considered statistically significant. Calculations were generated by SPSS software (version 26.0 for Windows, SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Baseline characteristics of the overall study population

A total of 354 patients who underwent TAVI with TAx as preferred access and 5980 patients who underwent TAVI with TF as primary access were included in this analysis (Supplemental Table 1). Median age was 80.0 (76.0–84.0) years in the TAx cohort versus 83.0 (78.0–86.0) in the TF cohort, and 49% versus 56% were women. The median EuroSCORE was 13.5 (IQR 9.0–21.9) for TAx versus 14.3 (IQR 9.0–22.2) for TF. In the TAx cohort more patients had prior myocardial infarction, previous PCI, previous stroke and peripheral artery disease. In the TF cohort more patients had chronic kidney disease with an eGFR <30 ml/min/1.73 m2. In the TAx cohort, mean aortic valve area was 0.75 ± 0.21 cm^2 versus 0.66 ± 0.19 cm^2 in the TF cohort. Mean and peak aortic valve gradients were 46 ± 15 mmHg versus 51 ± 17 mmHg ($p < 0.001$) and 76 ± 23 mmHg versus 81 ± 23 mmHg (p < 0.001) for TAx and TF, respectively. All patients received a self-expandable valve. In the TAx cohort 46 (13%) patients received a third-generation self-expanding valve, compared to 1579 (28%) of the patients in the TF cohort (Supplemental Table 1).

3.2. Baseline characteristics of the propensity matched cohort

After propensity score matching, 322 TAx patients were compared to 322 TF patients. In the propensity matched population, patients treated using the TAx access were similar to patients treated using the TF access with respect to age, gender, BMI, EuroSCORE, diabetes, myocardial infarction, previous CABG or PCI, peripheral artery disease, prior stroke, atrial fibrillation and the percentage of patients with an eGFR <30 ml/min/1.73 m2. Echocardiographic parameters were similar in both groups. The percentage of third generation devices was similar in both cohorts (Table 1).

3.3. Clinical outcomes in the overall study population

Patients in the TAx cohort had a similar procedural death rate (TAx 2% versus TF 2%, $p = 0.82$) and procedural success rate (TAx 91% versus TF 93%, $p = 0.13$) compared to the TF cohort. Conversion to surgery was more frequent in the TAx cohort (TAx 2% versus TF 1%, $p = 0.03$). In-hospital death rates, rates for stroke and transient ischemic attack as well as life-threatening bleeding were similar in both groups. There were more procedural myocardial infarctions (TAx 5% versus TF 1%, $p < 0.001$) and major bleedings (TAx 9% versus TF 6%, $p = 0.02$), but fewer new permanent pacemaker implantations (TAx 12% versus TF 20%, p < 0.001) in the TAx cohort (Supplemental Table 2).

3.4. Clinical outcomes in the propensity matched population

In the propensity matched population, similar rates were observed for procedural death <72 h (TAx 1% versus TF 2%, $p = 0.74$), conversion to surgery (1% in both groups, $p = 0.92$) and device success (TAx 91% versus TF 88%, $p = 0.29$).

In-hospital death (TAx 4% versus TF 3%, $p = 0.41$), stroke (TAx 2% versus TF 3%, $p = 0.19$), transient ischemic attack (TAx 1% versus TF 0,3%, $p = 0.73$), life-threatening bleeding (TAx 2% versus TF 3%, $p = 0.40$) and major bleeding (TAx 8% versus TF 9%, $p = 0.77$) were similar in both groups. Myocardial infarction rate in the TAx group significantly

Table 1
Baseline characteristics of patients undergoing transaxillary versus transfemoral transcatheter aortic valve implantation - propensity matched population.

	Transaxillary TAVI ($n = 322$)	Transfemoral TAVI (n = 322)	P-value	SMD
Age (years)	80 (76–84)	81 (76–85)	0.60	0.03
Female	160 (50%)	146 (45%)	0.27	0.09
BMI	26.3 (23.8–29.8)	26.0 (24.0–29.4)	0.99	0.04
Logistic Euroscore (%)	13.4 (9.0–21.5)	13.2 (8.4–19.0)	0.18	0.04
Medical History				
Diabetes Mellitus	107 (33%)	118 (37%)	0.36	0.08
Myocardial infarction	69 (21%)	71 (22%)	0.85	0.01
Previous PCI	118 (37%)	128 (40%)	0.42	0.07
Previous CABG	44 (14%)	41 (13%)	0.73	0.04
Atrial Fibrillation	80 (25%)	77 (24%)	0.78	0.03
Previous stroke or TIA	66 (21%)	76 (24%)	0.34	0.09
eGFR <30 ml/min/1.73 m2)	20 (6%)	30 (9%)	0.14	0.24
Peripheral artery disease	102 (32%)	111 (35%)	0.45	0.07
Echocardiography				
Aortic valve area (cm2)	0.74 ± 0.21	0.74 ± 0.21	0.78	0.02
Mean aortic valve gradient (mmHg)	46 ± 15	47 ± 16	0.27	0.09
Peak aortic valve gradient (mmHg)	76 ± 24	78 ± 25	0.40	0.07
Procedural characteristics				
Third generation valve	44 (14%)	55 (17%)	0.23	0.14
Year of procedure	2013 (2011–2014)	2013 (2012–2014)	0.96	0.01
Self-expandable valve	322 (100%)	322 (100%)	1.00	–

The propensity score included: age, gender, body mass index, history of myocardial infarction, history of percutaneous coronary intervention, history of coronary artery bypass graft, atrial fibrillation, history of stroke or transient ischemic attack, peripheral vascular disease, glomerular filtration rate < 30 ml/min/1.73m^2, aortic valve area, mean aortic valve gradient, peak aortic valve gradient, logistic EuroSCORE, year of TAVI procedure, and valve design (balloon or self-expandable). SMD: Standardized Mean difference.

exceeded that of the TF group (TAx 4% versus TF 1%, $p = 0.05$). New permanent pacemaker implantation rate was significantly higher in the TF group (TAx 12% versus TF 21%, $p = 0.001$). New permanent pacemakers were equally implanted in patients with newer generation valves, compared to older generation valves (15.2% vs 17.1%, $p = 0.63$).

At 30 days and 1-year follow-up, death occurred at similar rates (30 days: TAx 5% versus TF 6%, $p = 0.90$, 1 year: TAx 20% versus TF 16%, $p = 0.17$) (Table 2, Fig. 1).

4. Discussion

This is the first study comparing clinical outcomes in patients treated with TAVI using either the transfemoral or the transaxillary approach as preferred access. Our main findings are that first line transaxillary access is feasible and safe, with similar procedural success and peri-procedural death rates compared to TF access. Also, we report similar rates for stroke and TIA as well as life-threatening and major bleeding in the cohort compared to the TF cohort.

In the unmatched cohorts, there was a significant difference in peripheral artery disease (PAD) (Supplemental Table 1, 34% of TAx patients versus 13% of TF patients had peripheral artery disease $p \leq 0.001$). In the TAx cohort, the high prevalence of PAD might be the result of referral bias resulting in an overrepresentation of PAD. Furthermore, the presence of peripheral artery disease might preclude TF access in patients in the CENTER cohort, resulting in an underrepresentation of PAD in the TF cohort. However, in the matched cohorts the prevalence of PAD was similar in both cohorts (Table 1, 32% TAx versus 35% TF, $p = 0.45$, SMD 0.07).

Periprocedural and 30-day death rate as well as stroke rate were comparable in the TAx cohort compared to the TF cohort (periprocedural death: TAx 4% versus TF 3%, $p = 0.41$; 30 day mortalityTAx 5% versus TF 5%, $p = 0.90$; stroke TAx 2% versus TF 3%, respectively) and are in line with mortality- and strokerates published in the STS/ACC TVT registry from the same era [18]. A recent network meta-analysis comparing TF and TAx access showed higher rates of 30 day mortality, stroke, major bleeding and major vascular complication in TAx compared to TF access. However, the studies included in this meta-analysis were non-randomized and patients in TAx cohorts were mainly treated using TAx access because of prohibitive iliofemoral anatomy [19]. Therefore the extent of peripheral artery disease and comorbidities in our TAx cohort might be lower than that seen in earlier published TAx cohorts and more similar to that published in TF cohorts, resulting in outcome more similar to outcome for TF rather than TAx-alternative access.

In the trans-axillary cohort, significantly more peri-procedural myocardial infarctions were found. Of the 8 patients that were diagnosed with myocardial infarction, 5 had previous CABG with the LIMA in use as graft on the LAD. In these patients, the indwelling sheath overlying the ostial LIMA caused ischemia with enzymatic infarction and/or hemodynamic instability or ventricular fibrillation. One of these patients died in the intensive care unit after prolonged cardiogenic shock. Though early reports regarding transaxillary TAVI stated that a patent LIMA in use as coronary bypass graft was no contra-indication [6], these incidents necessitated a change of protocol in our institution as described earlier [15]. Of note, patients in this cohort were treated between 2009 and 2016. In this period, large outer diameter sheaths were used. With the current sheathless (and percutaneous) transaxillary approaches, the risk of myocardial infarction when using the transaxillary approach with a patent LIMA graft might be lower than we describe. Still, we consider a patent LIMA a contra-indication for use of the left axillary artery as TAVI access.

In the TAx cohort, significantly fewer new permanent pacemakers were implanted: 12% in the TAx cohort versus 21% in the TF cohort. The latter is similar to the new permanent pacemaker rate as published in the SURTAVI trial, in which a new permanent pacemaker was implanted in 25.9% of intermediate risk TAVI patients, of whom 93.6% were treated using iliofemoral access [20]. In registries of the CoreValve/Evolut R platform using TF access, pacemaker implant rates in patients were reported around 24% [21,22]. Our results are also in line with a systematic review which reported rates of 16.3–37.7% for early generation self-expandable devices. In newer generation self-expanding devices, pacemaker rates were as high as 14.7–26.7% [23]. The low permanent pacemaker implantation rate in the TAx cohort might theoretically be the result of a shorter working distance between the tip of the catheter and the sheath, less torque on the delivery system and therefore better steerability and control over the device during implantation. Furthermore, coming from the left axillary artery, the orientation in the LVOT might be more towards posterior. It should be noted though that previously published TAx series describe higher pacemaker implantation rates, more comparable to TF rates [6,11,14,24–26]. Moreover, the variability in regards with the indication for new permanent pacemaker implant in the TF centers could also explain the difference in pacemaker implantation rates.

In the TAx cohort, the axillary artery was the preferred access, irrespective of iliofemoral anatomy or disease and all patients were treated under general anesthesia. Currently in our center most patients are treated with percutaneous access via the transfemoral route with local anesthesia. TAx access is considered only when iliofemoral disease or tortuosity precludes TF access or is considered high risk. Furthermore, percutaneous TAx access using mild sedation is now a valid, safe and less invasive option.

Table 2
Clinical outcomes of patients undergoing transaxillary versus transfemoral transcatheter aortic valve implantation - propensity matched population.

	Transaxillary TAVI (n = 322)	Transfemoral TAVI (n = 322)	P-value
Procedural outcomes			
Death <72 h	4 (1%)	5 (2%)	0.74
Conversion to surgery	3 (1%)	4 (1%)	0.92
Device success	293 (91%)	202 (88%)	0.29
In hospital outcomes			
Death	14 (4%)	10 (3%)	0.41
Stroke	5 (2%)	10 (3%)	0.19
TIA	2 (1%)	1 (0.3%)	0.73
Life-threatening bleeding	5 (2%)	7 (3%)	0.40
Major bleeding*	27 (8%)	25 (9%)	0.77
Myocardial infarction	8 (4%)	4 (1%)	0.05
Permanent pacemaker implantation	39 (12%)	69 (21%)	0.001
30-day outcomes			
Death	15 (5%)	14 (5%)	0.90
One-year outcomes			
Death	64 (20%)	41 (16%)	0.17

* Major bleeding includes life-threatening bleeding.

5. Conclusion

This is the first matched comparison of preferred TAx versus preferred TF access in TAVI. The data show that preferred TAx access, irrespective of femoral anatomy, is feasible and safe with outcomes that are comparable to TF access in TAVI using self-expanding devices. In this study TAx access itself is not linked to worse outcome. Therefore, TAx access should be considered when TF access is not impossible but expected to be associated with high risk because of iliofemoral or aortic disease or extreme tortuosity.

6. Limitations

The TAx cohort is a single center cohort and though TAx was the default access, referral patterns from referring centers may have led to selection bias. In the TAx cohort, only self-expanding devices were implanted; therefore, for this analysis balloon-expandable devices were

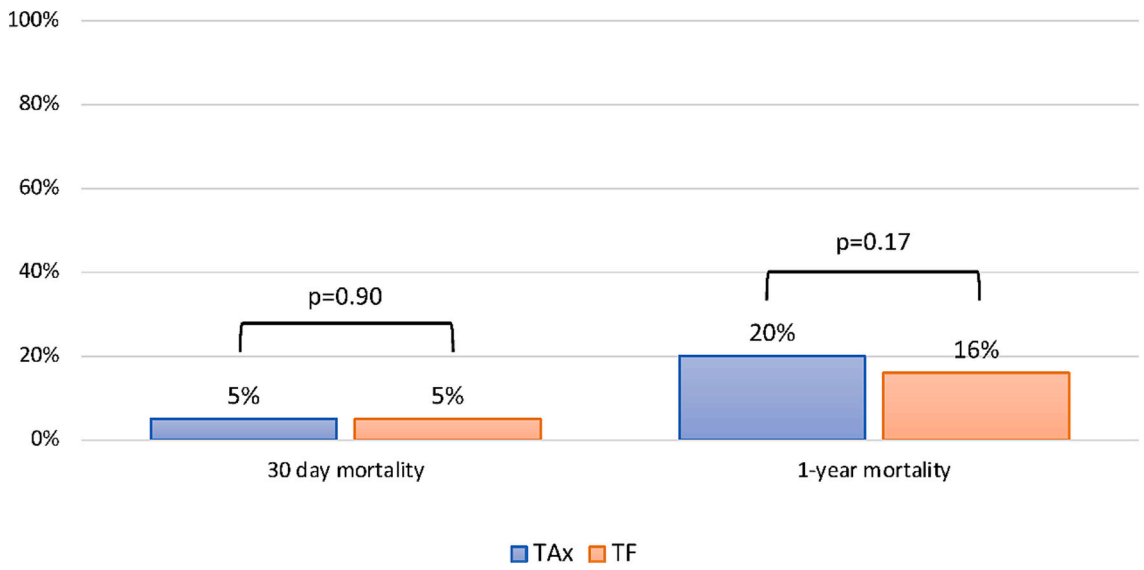

Fig. 1. All-cause mortality in the propensity matched population at 30 days and 1 year follow-up.
TAx: transaxillary access; TF: transfemoral access.

excluded from the CENTER study cohort. Furthermore, this was a non-randomized study, therefore results might be subject to selection bias and confounding. Minimizing these confounders by propensity matching does not preclude the presence of unmeasured confounding factors and heterogeneity could be increased because of strengthening of these unmeasured confounders.

Contributorship statement

MvW, AvN, RD, NvR contributed to the design of the study; AvN. and RD performed the statistical analyses of the data; MvW and AvN contributed equally to writing the manuscript. MvW, KvdW, MR, HG, MV, LvG, GG collected and analyzed the data for the TAx cohort. JAB, DT, FSDB, MB, RK, AL, ADO, FR, GD, RM, RD, collected and analyzed the data in the TF cohort. The manuscript was critically revised and approved by all authors. RD and NvR are the study guarantors.

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Conflict of interest statement

Dr. van Wely is a proctor for Abbott Vascular. Dr. van Nieuwkerk has no relevant disclosures. Dr. Rooijakkers has no relevant disclosures. Dr. van der Wulp has no relevant disclosures. Dr. Gehlmann is a proctor for Abbott Vascular and Medtronic. Dr. van Garsse is a proctor for Edwards Lifesciences. Dr. de Brito Jr. is a proctor for Edwards Lifesciences and Medtronic. Dr. Geuzebroek has no relevant dislclosures. Dr. Baz has no relevant disclosures. Dr. Tchétché has no relevant disclosures. Dr. De Brito Jr. has no relevant disclosures. Dr. Barbanti is consultant for Edwards Lifesciences and received speaker honoraria from Medtronic and Biotronik. Dr. Kornowski has no relevant disclosures. Dr. Latib is a consultant for Medtronic and has received honoraria from Abbott Vascular. Dr. D'Onofrio is a proctor for Edwards Lifesciences and for Symetis. Dr. Ribichini has no relevant disclosures. Dr. Dangas has no relevant disclosures. Dr. Mehran has no relevant disclosures. Dr. Delewi has no relevant disclosures. Dr. van Royen received research grants from Abbott Vascular, Philips, and Biotronik, speaker honoraria from Abbott Vascular and is consultant for Medtronic, Rainmed and Castor.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.131353.

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