Catheterization and Cardiovascular Interventions

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ORIGINAL ARTICLE - CLINICAL SCIENCE OPEN ACCESS

Extremity Function After Transfemoral Transcatheter Aortic Valve Implantation: A TAVI XS Sub-Study

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Received: 12 November 2025 | **Revised:** 22 December 2025 | **Accepted:** 5 January 2026

Funding: Medtronic Europe, Grant/Award Number: A 1678426/SVZ

Keywords: aortic stenosis | Lower-Extremity Function Scale (LEFS) | Quick Disabilities of the Arm, Shoulder, and Hand (Quick DASH) | secondary access | TAVI XS

ABSTRACT

Background: Physical decline after transcatheter aortic valve implantation (TAVI) is associated with worse outcomes. However, data on post-TAVI extremity function are limited. This sub-study of the TAVI XS trial aimed to assess extremity function after transfemoral TAVI, evaluate functional decline, compare outcomes between upper-and lower-extremity secondary access approaches and identify predictors of functional decline after TAVI.

Methods: The TAVI XS was a randomized clinical trial comparing upper- and lower-extremity secondary access during TAVI. Patients were assessed for extremity function at baseline and at 30 days using the Lower Extremity Function Scale (higher score indicating better function) and the Quick Disabilities of the Arm, Shoulder, and Hand questionnaire (higher score indicating worse function).

Results: Lower-extremity (45.0 [IQR 35.0–57.0] to 52.0 [39.0–63.0]; $p < 0.001$), and upper-extremity function (11.4 [2.3–25.0] to 6.8 [0–22.7]; $p = 0.003$) improved after TAVI. Relevant decline in lower-extremity function occurred in 20 (8.4%) patients, and in upper-extremity function in 19 (8.0%) patients. No differences in post-TAVI function were observed between upper- or lower-extremity secondary access (lower-extremity: 10.1% vs. 6.7%; $p = 0.35$, upper-extremity: 7.6% vs. 8.4%; $p = 0.81$). Predictors (OR [95% CI]) of clinically relevant decline were baseline use of dual antiplatelet therapy/oral anticoagulants (4.17 [1.39–12.49]; $p = 0.01$) for lower-extremity function and multiple punctures (4.05 [1.46–11.24]; $p = 0.007$) for upper-extremity function. Age inversely affected lower- (0.92 [0.85–0.99/year]; $p = 0.02$) and upper-extremity function (0.93 [0.86–0.99/year]; $p = 0.04$).

Conclusions: The incidence of clinically relevant decline in extremity function after TAVI is low. No differences in reported extremity function were observed between the upper- and lower-extremity secondary access approach. Predictors of decline were antithrombotic therapy and multiple punctures.

Trial Registration: ClinicalTrials.gov identifier: NCT05672823.

1 | Introduction

Physical decline during the index hospitalization has been associated with poorer long-term outcomes following transcatheter aortic valve implantation (TAVI) [1]. While the mechanisms behind this decline are complex and multifactorial, a decline in extremity function may be a significant contributing factor. Previously, access site-related extremity dysfunction after percutaneous coronary intervention (PCI) has been investigated. These studies, particularly focusing on small-bore transradial and transfemoral access, have shown that clinically significant decline in extremity function after PCI occurs infrequently [2–4]. However, during TAVI, multiple access sites are required, including a 14–22 French primary access for introduction of the valve prosthesis. Unsurprisingly, vascular and access site-related complications, such as bleeding, occur much more frequently after TAVI as compared to PCI [5–8]. Consequently, a decline in extremity function after TAVI might affect a considerable number of patients, but no data are currently available in the literature.

The current study is a prespecified sub-study of the TAVI XS Trial, which compared an upper-extremity approach for secondary access during TAVI with a lower-extremity approach. The TAVI XS demonstrated that clinically relevant secondary access site-related bleeding complications were reduced by using the upper-extremity as compared to the lower-extremity for secondary access [9]. To address the current gap in knowledge and assess whether the secondary access approach affects extremity function after TAVI, this sub-study was prespecified. The study aims to one, investigate extremity function after TAVI; two, assess the incidence of clinically relevant decline in extremity function after TAVI; three, compare extremity function between the upper-extremity approach and the lower-extremity approach for secondary access; and finally, identify potential predictors of relevant decline in extremity function after TAVI.

2 | Methods

2.1 | Study Design

The TAVI XS trial was an investigator-initiated, multicenter, randomized clinical trial comparing an upper-extremity approach for secondary access with the predominantly used lower-extremity approach. It primarily aimed to compare the rate of secondary access site-related bleeding events between both approaches in transfemoral TAVI (TF-TAVI). The trial was performed in four high-volume TAVI centers in the Netherlands. In all patients transfemoral access was used for the delivery of the TAVI device. However, for diagnostic access and possible temporary pacing lead placement (in case pacing over the wire was not used), patients were randomized to the upper-extremity approach (using the radial artery and when applicable the upper arm veins) or the lower-extremity approach (using the contralateral femoral artery and when applicable the femoral vein). The trial design and the main results were published previously [9, 10].

The TAVI XS trial was designed in accordance with the Declaration of Helsinki and was approved by the Medical Research Ethics Committee (MREC) Oost-Nederland and the institutional review board of each participating site. This research was supported by a research grant from Medtronic (grant number A1678426/SVZ). Medtronic was not involved in the design or monitoring of the trial; the enrollment of participants; the collection, recording, storage, retention, or analysis of the data; the writing of the manuscript; or the decision to submit the manuscript for publication.

2.2 | Participants

All patients enrolled in the TAVI XS trial were included in this sub-study. Patients were deemed eligible for participation in the TAVI XS trial if they were 18 years of age or older, provided written informed consent, and were scheduled for TF-TAVI. Patients were excluded from participation if a contraindication for upper arm- or femoral venous access or a contraindication for radial- or femoral arterial access was present. Patients in whom there was intent to use a cerebral embolic protection device requiring an additional arterial access were also excluded.

2.3 | TAVI Procedure

TAVI was performed following local protocol and (inter) national guidelines. All patients were treated using a transfemoral approach for primary access and were randomized to either an upper- or lower-extremity approach for the secondary access sites. Ultrasound (US) guidance was used for femoral artery and vein access, as well as for upper-arm venous access [11, 12]. The use of US guidance for radial access and the choice of primary- and secondary-access closure methods were left to the discretion of the operator.

2.4 | Objectives

The primary objective of this sub-study was to investigate upper- and lower-extremity function at baseline and 30 days after TAVI. Secondary objectives were to assess clinically relevant decline in extremity function at 30 days after TAVI, and to compare extremity function between the upper- and lower-extremity cohorts, as investigated in the TAVI XS trial. A final objective was to identify potential predictors of clinically relevant decline in extremity function after TAVI.

2.5 | Procedures and Materials

Lower- and upper-extremity function were assessed by making use of two validated questionnaires that were filled out by the trial participants at baseline and at 30-day follow-up. The same assessment scales were used for both upper- and lower-extremity cohorts.

Lower-extremity function was assessed using the "Lower-Extremity Function Scale" (LEFS). The LEFS is a 20-item questionnaire that evaluates lower-extremity function based on the difficulty participants experience when performing daily physical activities, such as walking or climbing stairs. Each item is scored on a 5-point scale ranging from extreme difficulty or inability to perform a task (0 points) to having no difficulty in performing the task (four points). Scores range from 0 (extreme functional impairment) to 80 points (no functional impairment). The test demonstrates good test-retest reliability across a

spectrum of lower-extremity disorders and chronic conditions [13].

Extremity dysfunction was defined as a clinically relevant decline in extremity function and was assessed by using the minimal clinically important difference (MCID) score. The MCID for the LEFS varies across patient categories and sources. The MCID that is conventionally used is nine points, although higher numbers have been reported for specific disorders [13, 14]. For this sub-study, MCID thresholds of both 9 and 12 points were used for the LEFS.

Upper-extremity function was assessed using the "Quick Disabilities of the Arm, Shoulder, and Hand" (Quick DASH) questionnaire [15]. The Quick DASH questionnaire has previously been applied in the assessment of upper-extremity dysfunction after radial puncture in PCI [16, 17]. The Quick DASH comprises 11 questions detailing specific complaints (e.g., pain and tingling sensations) and daily activities (e.g., opening a jar or using a knife to cut food). The answer scale is a 5-point scale ranging from no complaints or trouble performing the task (one point), to extreme complaints or not being able to perform said task (five points). The questionnaire results were deemed valid if at least 10 out of 11 questions had been answered. The Quick DASH score was calculated by adding up all item scores, divided by the respective number of questions that were answered, subtracting one, and multiplying the score by 25. By doing so a total Quick DASH score, ranging from 0 to 100 points, was obtained. A higher total Quick DASH score signified more extensive impairment of upper-extremity function. An MCID of 15.91 was previously reported and suggested to be used as lower threshold for the Quick DASH [18]. Due to variability in reported MCIDs across studies and patient populations [18–20], we used the MDC95 (minimal detectable change at the 95% confidence level) score of 20 points as a proxy for the upper threshold of the MCID [21].

2.6 | Endpoints

The primary endpoints were the LEFS and Quick DASH scores at 30-day follow-up compared to baseline. Secondary endpoints included the incidence of clinically relevant decline in both lower- and upper-extremity function at 30 days after TF-TAVI, using the proposed MCID scores, and the comparison of the upper- and lower-extremity approach for secondary access with regard to extremity function scores and relevant decline. Additionally, predictors of clinically relevant decline in extremity function were assessed, with specific attention to access-site-related complications. Finally, sub-group analyses were conducted regarding extremity function. These analyses included the as-treated population, comprising patients with successful secondary access, along with separate sub-group analyses of patients who experienced secondary access failure, and of those treated with expandable versus non-expandable introducers for the primary access site.

2.7 | Statistical Analyses

The primary analyses included the intention-to-treat population of the TAVI XS trial. Within-group differences, comparing follow-up scores to baseline scores, were assessed using the paired samples *t*-test for normally distributed data and the Wilcoxon signed-rank test for non-normally distributed data. Normally distributed continuous data are presented as mean (±SD), and non-normally distributed data are presented as median (IQR).

The incidence of clinically relevant decline in extremity function was compared between groups using Pearson's chi-square test or Fisher's exact test (where appropriate). The incidence of clinically relevant decline in extremity function was assessed and compared for both the lower and upper MCID thresholds for extremity dysfunction. Predictors of relevant decline in extremity function were assessed using logistic regression. Univariable logistic regression was used to determine the individual effects of the chosen variables and to screen for possible predictors. To create a multivariable model, a purposeful selection of variables was applied [22]. Variables with a p-value < 0.4 in the univariable analyses were included in the multivariable model. This threshold was chosen to minimize the risk of overfitting while ensuring that potentially relevant variables were not excluded. Following variable selection, multivariable logistic regression was applied. These steps were performed separately for both lower- and upper-extremity function.

A two-tailed p-value < 0.05 was considered statistically significant for all tests. Data analyses were performed using SPSS Statistics version 29 (IBM Corp, Armonk, NY, USA).

3 | Results

3.1 | Study Population and TAVI Procedure

A total of 238 patients were enrolled in the TAVI XS trial between December 2022 and December 2023. Patients were randomly assigned to either an upper-extremity approach for secondary access ($n = 119$ [50%]) or a lower-extremity approach for secondary access ($n = 119$ [50%]). Baseline and procedural characteristics have been published previously [9]. The mean age was 79.4 (±6.5) years, and the majority of patients were male (150/238; 63.0%). Left ventricular stiff-wire pacing was used in 145 patients (60.9%), and a temporary pacing lead was placed in 93 patients (39.1%). Secondary access site failure occurred in 14 patients (11.8%) in the upper-extremity cohort and in one patient (0.8%) in the lower-extremity cohort. In the upper-extremity cohort, the majority of access site failures were related to secondary arterial access ($n = 8$), two were due to secondary venous access failure, and four patients experienced failure of both secondary access sites. Primary access site closure was achieved using a closure device in all but two patients ($n = 236$, 99.2%). In most cases the device used was the suture based Perclose Proglide ($n = 135$, 56.7%) (Abbott, Illinois U.S.), and in the remainder a MANTA device (Teleflex inc., Pennsylvania, U.S.) was used ($n = 101$, 42.4%). Secondary arterial access closure was predominantly obtained using either an Angio-Seal ($n = 115$, 48.3%) or TR-band ($n = 108$, 45.4%) (both Terumo Corp., Tokyo, Japan), depending on randomization arm.

Clinically relevant bleeding (i.e., bleeding academic research consortium [BARC] type 2, 3, or 5 bleeding) occurred in 66 patients (27.7%), and 21 bleeding events were related to the randomized secondary access. Secondary access site-related bleeding complications occurred significantly more frequent in

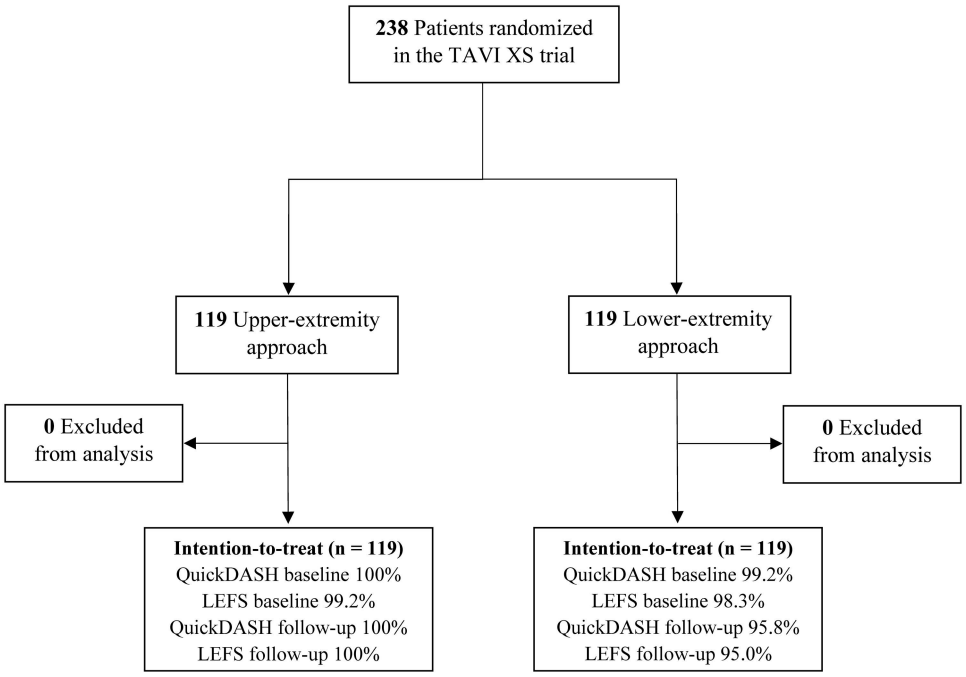


FIGURE 1 | Flowchart of the study demonstrating completeness and validity of study questionnaires.

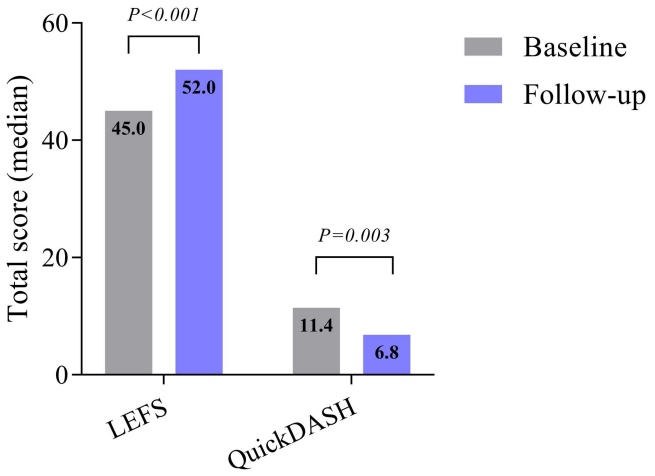


FIGURE 2 | Lower- and upper-extremity function after TAVI assessed using the LEFS and Quick DASH questionnaires, comparing 30-day follow-up to baseline scores. [Color figure can be viewed at wileyonlinelibrary.com]

the lower-extremity cohort compared to the upper-extremity cohort (16 vs. 5 events; $p = 0.1$), and most bleeding events were related to the secondary arterial access site (85.7%). The median time to mobilization was 445 min (IQR 286–1254), and the median duration of hospitalization was 4 days (IQR 2–5) for the total cohort.

3.2 | Questionnaires

Response rates with valid questionnaires are displayed in Figure 1. Baseline LEFS questionnaires were valid for 118 (99.2%) and 117 patients (98.3%) for the upper- and lower-extremity group respectively, while follow-up LEFS questionnaires were analyzable for 100% (119/119) and 95% (113/119) of patients. The baseline Quick DASH questionnaire was analyzable for all patients in the upper-extremity group and for 118 (99.2%) patients in the lower-extremity group. Similarly, the follow-up Quick DASH questionnaire validity for the upper-extremity group was 100% and was 95.8% (114/119) for the lower-extremity group.

3.3 | Lower-Extremity Function

For the total cohort, the baseline median LEFS score was 45.0 (IQR 35.0–57.0) and at 30-day follow-up, the median LEFS score was 52.0 (IQR 39.0–63.0) ($p \leq 0.001$) (Figure 2). On an individual level, the majority of patients experienced either no change (15/238; 6.3%) or an improvement (152/238; 63.9%) in perceived lower-extremity function at 30-day follow-up compared to baseline. Clinically relevant decline in lower extremity function at 30 days was observed in 20 (8.4%) patients after transfemoral TAVI when applying the lower MCID threshold of nine points, and in 14 (5.9%) patients when using the upper MCID threshold of 12 points.

3.4 | Upper-Extremity Function

The median Quick DASH score at baseline was 11.4 (IQR 2.3–25.0) and improved at 30-day follow-up (median Quick DASH score 6.8 [IQR 0.0–22.7]) ($p = 0.003$) (Figure 2). Similar to lower-extremity function, the majority of patients experienced either no change (69/238; 29.0%) or improvement (105/238; 44.1%) in upper-extremity function at 30-day follow-up. Clinically relevant decline in upper-extremity function was observed in 19 (8.0%) patients 30 days after TF-TAVI when the lower threshold (MCID $\geq$ 15.91) was applied, and in 15 (6.3%) patients when applying an MCID $\geq$ 20.

3.5 | Comparing the Upper- and Lower-Extremity Approach for Secondary Access

When comparing lower-extremity function for both treatment strategies for secondary access, the median LEFS score at baseline (47 [IQR 35.0–57.3] vs. 44 [IQR 34.5–57.5]; $p = 0.55$) and follow-up (52 [IQR 41.0–63.0] vs. 52 [IQR 38.0–63.0]; $p = 0.59$) were comparable for the upper- and lower-extremity group (Table 1, Figure 3). Twelve (10.1%) patients in the upper-extremity group and eight (6.7%) patients in the lower-extremity group experienced relevant decline in lower-extremity function when the lower threshold (MCID ≥ 9) was applied ($p = 0.35$). Similarly, no differences were found in the incidence of relevant decline in lower-extremity function when the upper threshold (MCID ≥ 12) was applied (8 [6.7%] vs. 6 [5.0%] patients; $p = 0.58$).

Similar results were observed for upper-extremity function. The median baseline Quick DASH score was 11.4 (IQR 2.3–25.0) for both the upper- and lower-extremity groups ($p = 0.54$). Moreover, at the 30-day follow-up, there was no difference in Quick DASH scores between both groups (6.8 [IQR 2.3–20.5] vs. 6.8 [IQR 0–22.7]; $p = 0.89$) (Table 1, Figure 3). Clinically relevant decline in upper-extremity function was observed in 9 (7.6%) patients in the upper-extremity group compared with 10 (8.4%) patients in the lower-extremity group (MCID ≥ 15.91; $p = 0.81$). When the upper threshold (MCID ≥ 20) was applied, both treatment groups showed similar rates of decline in upper-extremity function (7 [5.9%] vs. 8 [6.7%] patients; $p = 0.79$).

3.6 | Predictors of Decline in Extremity Function

Uni- and multivariable analyses of possible predictors revealed that the use of dual antiplatelet therapy (DAPT) or oral anticoagulants (OAC) at baseline (multivariable odds ratio (OR) 4.17, 95% CI 1.39–12.49; $p = 0.01$) was associated with clinically relevant decline in lower-extremity function at 30 days (Table 2). Also, a trend was observed for patients in whom secondary access failure occurred (OR 3.86, 95% CI 0.90–16.52, $p = 0.07$). Multiple punctures for secondary access were associated with clinically relevant decline in upper-extremity function at 30 days (multivariable OR 4.05, 95% CI 1.46–11.24; $p = 0.007$). In addition, age was inversely associated with both a significant decline in lower-extremity function (multivariable OR 0.92, 95% CI 0.85–0.99 for every year increase in age; $p = 0.02$) as well as upper-extremity function (multivariable OR 0.93, 95% CI 0.86–0.99 for every year increase in age; $p = 0.04$) at 30 days (Table 2).

TABLE 1 | Extremity function for total cohort, and upper- and lower-extremity secondary access cohorts.

	Total cohort *N = 238*	Upper-extremity approach *n = 119*	Lower-extremity approach *n = 119*	*p* value
Lower-extremity function				
LEFS score baseline	45.0 (35.0–57.0)	47.0 (35.0–57.3)	44.0 (34.5–57.5)	0.55
LEFS score follow-up	52.0 (39.0–63.0)	52.0 (41.0–63.0)	52.0 (38.0–63.0)	0.59
Relevant decline (MCID 9)	20 (8.4)	12 (10.1)	8 (6.7)	0.35
Relevant decline (MCID 12)	14 (5.9)	8 (6.7)	6 (5.0)	0.58
Upper-extremity function				
Quick DASH score baseline	11.4 (2.3–25.0)	11.4 (2.3–25.0)	11.4 (2.3–25.0)	0.54
Quick DASH score follow-up	6.8 (0.0–22.7)	6.8 (2.3–20.5)	6.8 (0–22.7)	0.89
Relevant decline (MCID 15.91)	19 (8.0)	9 (7.6)	10 (8.4)	0.81
Relevant decline (MCID 20)	15 (6.3)	7 (5.9)	8 (6.7)	0.79

Note: Data are presented as median (interquartile range), or as number (%).
Abbreviations: LEFS, Lower Extremity Function Scale; MCID, minimal clinically important difference; Quick DASH, Quick Disabilities of the Arm, Shoulder and Hand questionnaire.

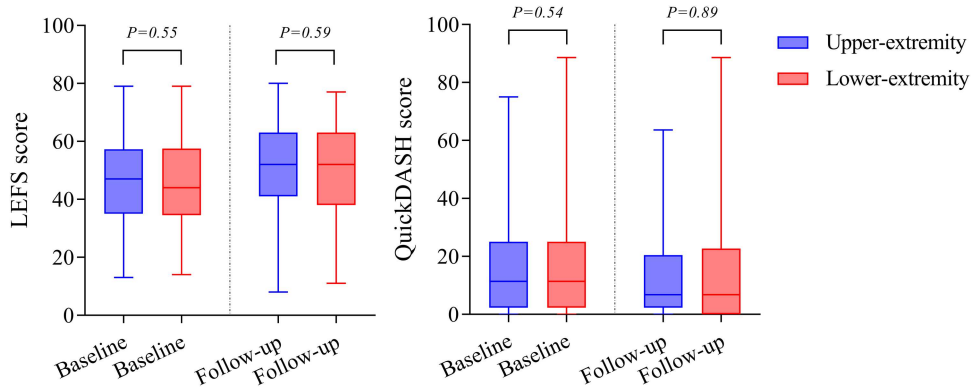


FIGURE 3 | Comparison of both approaches (upper- and lower-extremity approach) for secondary access during TAVI for both lower- and upper-extremity function. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 | Predictors of significant decline in extremity function.

Variables	Univariable analysis OR (95% CI)	*p* value	Multivariable analyses OR (95% CI)	*p* value
Lower-extremity dysfunction				
Age	0.94 (0.88–1.01)	0.07	0.92 (0.85–0.99)	**0.02**
Female sex	1.15 (0.45–2.93)	0.77		
Use of DAPT or OAC at baseline	2.97 (1.10–8.01)	0.03	4.17 (1.39–12.49)	**0.01**
Obesity (BMI > 30 kg/m^2)	0.91 (0.29–2.85)	0.87		
Diabetes	1.16 (0.42–3.15)	0.78		
Peripheral artery disease	1.24 (0.27–5.75)	0.79		
Ultrasound guided secondary access	2.54 (0.57–11.34)	0.22	4.36 (0.73–25.93)	0.11
> 1 puncture required for secondary access	1.02 (0.32–3.20)	0.98		
Secondary access failure	3.03 (0.78–11.78)	0.11	3.86 (0.90–16.52)	0.07
Bleeding of randomized secondary access (≥ BARC type 2)	1.16 (0.25–5.40)	0.85		
Bleeding of primary access (≥ BARC type 2)	0.94 (0.30–2.93)	0.91		
Major access site-related vascular complication	5.32 (1.26–22.45)	0.02	3.28 (0.60–17.89)	0.17
Time to mobilization	1.00 (1.00–1.00)	0.99		
Duration of hospitalization	1.07 (0.99–1.15)	0.10	1.05 (0.96–1.15)	0.30
Upper-extremity dysfunction				
Age	0.93 (0.87–0.99)	0.03	0.93 (0.86–0.99)	**0.04**
Female sex	1.60 (0.62–4.09)	0.33	1.60 (0.56–4.52)	0.38
Use of DAPT or OAC at baseline	1.32 (0.52–3.38)	0.56		
Obesity (BMI > 30 kg/m^2)	1.34 (0.46–3.92)	0.59		
Diabetes	1.25 (0.46–3.45)	0.66		
Peripheral artery disease	0.59 (0.07–4.63)	0.61		
Ultrasound guided secondary access	0.72 (0.25–2.12)	0.56		
> 1 puncture required for secondary access	4.29 (1.63–11.26)	0.003	4.05 (1.46–11.24)	**0.007**
Secondary access failure	3.23 (0.83–12.65)	0.09	3.03 (0.66–13.97)	0.16
Bleeding of randomized secondary access (≥ BARC type 2)	1.24 (0.27–5.77)	0.79		
Major access site-related vascular complication	3.10 (0.61–15.78)	0.17	2.77 (0.45–17.14)	0.27
Duration of hospitalization	1.06 (0.98–1.15)	0.17	1.05 (0.96–1.15)	0.33

Note: Bold values are statistically significant.
Abbreviations: BARC, Bleeding Academic Research Consortium; BMI, body mass index; DAPT, dual antiplatelet therapy; OAC, oral anticoagulation.

3.7 | Sub-Group Analyses for Extremity Function

A separate as-treated analysis was performed for patients with successful secondary access, including 102 patients in the upper-extremity cohort and 120 patients in the lower-extremity cohort. The results of the as-treated analysis were consistent with those of the primary intention-to-treat analysis (Supporting Information S1: Table 1). Patients experiencing access site failure showed similar baseline and follow-up extremity function scores, however, a trend was observed toward an increased rate of clinically relevant decline in both upper- and lower-extremity function at 30 days (Supporting Information S1: Table 2). Finally, a sub-group analysis was performed regarding the use of expandable introducers for the primary TAVI access. This analysis revealed a lower baseline LEFS score in the expandable group (43.0 [32.0–54.0] vs. non-expandable 50.0 [35.8–61.0]; $p = 0.02$) and a lower follow-up LEFS score (50.0 [37.0–61.0] vs. non-expandable 56.0 [42.3–64.0]; $p = 0.01$). However, no differences were observed in the occurrence of clinically relevant decline in extremity function (Supporting Information S1: Table 3).

4 | Discussion

The presented sub-study of the randomized clinical TAVI XS trial investigated extremity function after TAVI using these

randomized data and comparing both treatment strategies investigated in the TAVI XS trial. To our knowledge, this study is the first study investigating lower- and upper-extremity function after TF-TAVI.

Key findings can be summarized as follows: first, overall lower and upper-extremity function improved at 30-days after TAVI. Second, only ~8% of patients experienced a clinically relevant decline in lower- or upper-extremity function. Third, there was no difference in extremity function between the two treatment groups as investigated in the TAVI XS trial. Fourth, younger age was associated with clinically relevant decline in both lower- and upper-extremity function at 30 days. Moreover, baseline DAPT or OAC use was associated with clinically relevant decline in lower-extremity function at 30 days, while the need for multiple punctures was associated with a clinically relevant decline in upper-extremity function at 30 days.

Upper-extremity function following cardiac procedures has previously been investigated, especially after the introduction of the transradial approach for coronary angiography and PCI. In the prospective ACRA study, upper-extremity function after transradial coronary catheterization was assessed using the Quick DASH questionnaire [2]. No significant change in upper-extremity function was observed at 30-day follow-up and clinically relevant decline was observed in 6.3% of patients (MCID = 14). Similarly in a sub-study of the COLOR trial, investigating extremity function after large-bore transradial versus transfemoral access for PCI, relevant decline in upper-extremity function was observed in 6% of patients after a transradial approach when using an MCID of 14 points [16]. These findings are very similar to those observed in the present study. Using a slightly more conservative MCID (15.91 points), upper-extremity dysfunction after transradial secondary access occurred at a rate of 7.6%. These data suggest that the effect of a transradial approach for secondary access in TAVI on reported upper-extremity function is comparable to its effect in coronary catheterization. These findings are of importance, as we have previously demonstrated that an upper-extremity approach for secondary access in TAVI reduces access site-related bleeding complications. This approach, therefore, is likely the preferable approach for the majority of TAVI patients. Despite TAVI procedures being performed in a population characterized by increased frailty and greater comorbidity compared to PCI, our findings show that relevant decline in upper-extremity function after a transradial approach for secondary access occurs infrequently.

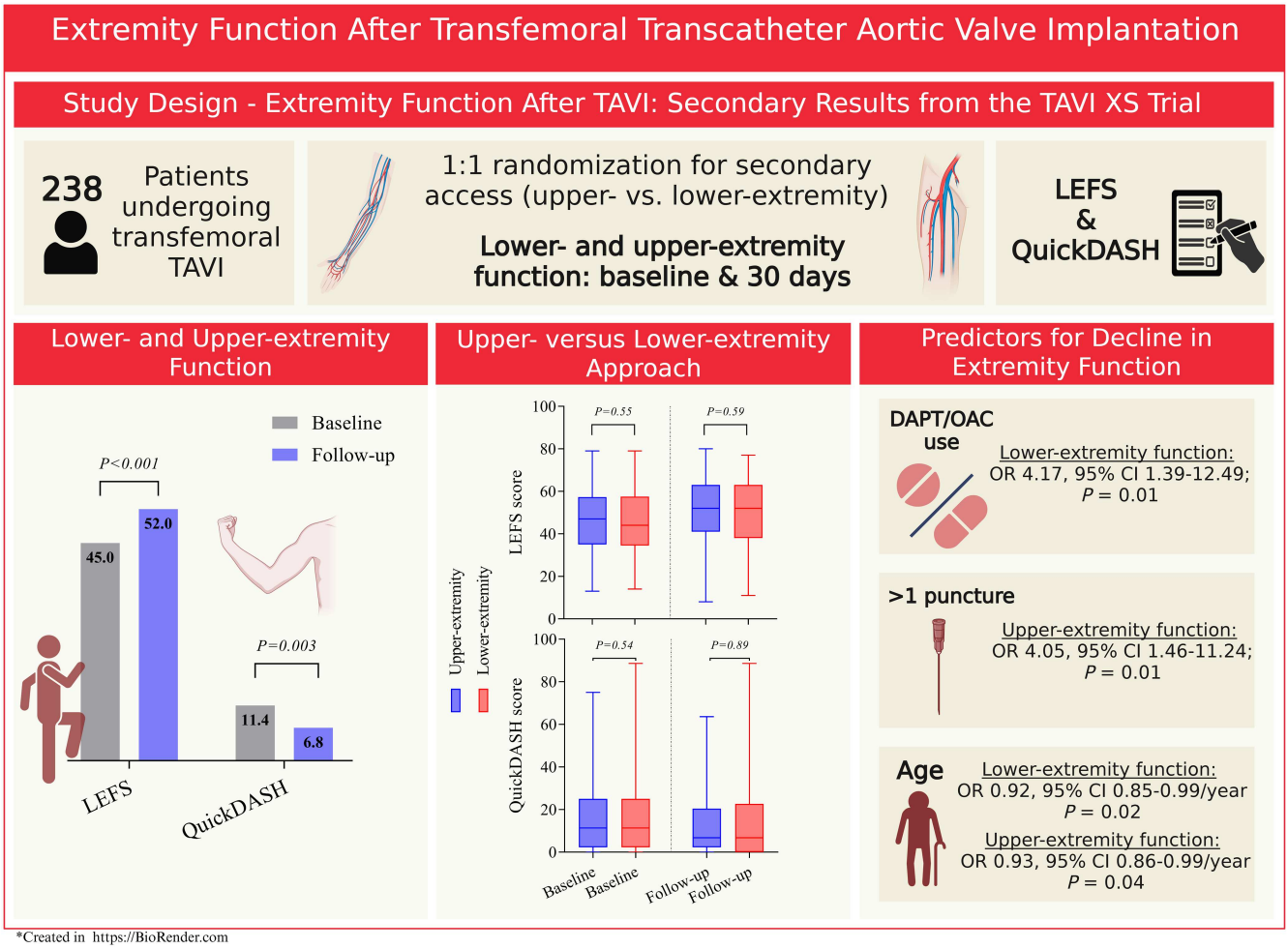
Data on lower-extremity function after coronary catheterization are more scarce. A review on extremity dysfunction following catheterization reported on four studies investigating lower-extremity dysfunction after transfemoral access for catheterization [23]. However, none of these studies used the LEFS questionnaire to systematically assess extremity function. The previously mentioned sub-study of the COLOR trial provides randomized data on lower-extremity function after large-bore femoral access. On a group-level, median LEFS scores did not change following 30 days of follow-up, and clinically relevant decline in lower-extremity function was observed in 11% of patients (MCID of 9). Similarly, in our study, no decrease in self-reported lower-extremity function was observed for the total cohort, with clinically relevant decline occurring in only 8.4% of patients. The observed difference in extremity dysfunction rates between the two studies should be appraised with caution, as these trials are difficult to compare. As an example, the COLOR trial investigated patients undergoing PCI rather than TAVI, a procedure which in general is performed in a dissimilar population. This distinction is reflected by the baseline LEFS scores, which were notably higher in the COLOR sub-study (59 points) when compared to our study (45 points). These findings could partially explain the observed difference in extremity dysfunction, as a lower baseline score reduces the likelihood of an absolute decrease of nine points at follow-up.

The paucity of data on lower-extremity function after TF-TAVI, particularly in light of its increasing use in a younger and lower-risk population, stresses the importance of our findings. Our results show that TF-TAVI, despite requiring a large primary access site, does not frequently result in patients experiencing clinically relevant lower-extremity dysfunction. Although the TAVI XS trial demonstrated an increased rate of secondary access-site related bleeding in the lower-extremity cohort, no differences in lower-extremity dysfunction were observed when compared to the upper-extremity cohort. This may be explained by the similar primary access strategy used in both cohorts and suggests that the large-bore primary femoral access is an important contributing factor to the occurrence of lower-extremity dysfunction.

Several predictors of clinically relevant decline in extremity function were identified. Baseline use of DAPT or OAC was associated with a relevant decline in lower-extremity function at 30 days. The use of DAPT or OAC may have increased minor bleeding complications that were deemed clinically irrelevant (i.e., BARC type 1 bleeding) in the TAVI XS trial. Although considered clinically irrelevant, these minor bleedings could have led to local swelling, discomfort, or limited mobility, thus increasing the perceived rate of extremity dysfunction among participants.

DAPT is usually given in TAVI patients after PCI for concomitant coronary artery disease. The ongoing PRO-TAVI trial is investigating whether deferral of routine PCI is noninferior to TAVI with PCI [24]. Omitting PCI, and thus the need for DAPT, pre-TAVI could be favorable for extremity function after TAVI, in addition to reducing potential bleeding complications. Regarding OAC, the POPular PAUSE TAVI trial recently demonstrated that periprocedural continuation of oral anticoagulation was not noninferior to the interruption of these therapies with regard to a composite of several major cardiac adverse events [25]. Moreover, continuation of these therapies resulted in an increased rate of bleeding. These findings support a strategy in which oral anticoagulants are temporarily discontinued prior to the TAVI procedure for most patients. Our current findings suggest that such a strategy might also help reduce the incidence of lower-extremity dysfunction after TF-TAVI.

Multiple punctures for secondary access were associated with relevant decline in upper-extremity function at 30 days. Multiple punctures may have caused increased pain and disability during follow-up due to an increased chance of damaging structures in the direct proximity of the upper arm vessels that were punctured. However, the need for multiple punctures might also reflect characteristics of patients who were more prone to develop extremity dysfunction in the first place, possibly due to more severely calcified or atherosclerotic vessels. This is also reflected in the observation that patients in the upper-extremity cohort who experienced access site failure and thus required multiple punctures showed a trend toward a greater incidence of both upper- and



CENTRAL ILLUSTRATION 1 | Extremity function after TAVI: secondary results from the TAVI XS trial. [Color figure can be viewed at wileyonlinelibrary.com]

lower-extremity dysfunction, despite the eventual successful lower-extremity secondary access.

Age was inversely associated with both a clinically relevant decline in lower- as well as upper-extremity function. These findings could potentially be explained by the nature of the questionnaires as both lower- and upper-extremity function were assessed based on physical activity. Additionally, the MCIDs that were used, were absolute rather than relative values, meaning that participants scoring poorly at baseline would require a similar reduction in questionnaire scores as those with higher baseline scores. Older patients potentially were less physically active at baseline and therefore might have been less likely to experience a significant decline in reported extremity function at 30-day follow-up.

4.1 | Limitations

The study has some limitations. First, although the TAVI XS trial was a randomized clinical trial, the qualitative nature of the outcome measures in this sub-study makes the results vulnerable to bias. Recall bias may have influenced the results as the success of the intervention could have affected the responses from participants. Moreover, all research using questionnaires is prone to non-response bias. However, the chance for non-response bias was likely low in the present study, given the high response rates.

Second, neither the LEFS nor the Quick DASH has been validated in a TAVI population. Therefore, the MCIDs that were applied might not have been optimal cut-off values for this population. Finally, while the TAVI XS trial was a funded, randomized clinical trial, the funder had no involvement in the trial design or in the writing of the manuscript.

5 | Conclusion

In this TAVI XS sub-study we demonstrated that lower- and upper-extremity function after TF-TAVI remains unaffected or improves for most patients. Moreover, the incidence of clinically relevant decline in lower- and upper-extremity function after TF-TAVI is low and is comparable between the upper-extremity and lower-extremity approach for secondary access. Younger age was associated with clinically relevant decline in both lower- and upper-extremity function, baseline DAPT or OAC use was associated with decline in lower-extremity function, and the need for multiple punctures was associated with decline in upper-extremity function at 30-days. (Central Illustration 1).

Acknowledgments

The authors gratefully acknowledge the valuable support of F. Vedder and K. van Miert, MSc, in data entry. This work was supported by a Research Grant from Medtronic (grant number A 1678426/SVZ).

Disclosure

Marleen H. van Wely reported receiving personal fees from Abbott Vascular and Boston Scientific Corporation. Robert Jan van Geuns reported receiving consulting and speaker's fees from Abbott Vascular, AstraZeneca, Sanofi SA, Amgen Inc, and InfraRedx Inc and receiving institutional research grant funding from Amgen Inc, InfraRedx Inc, AstraZeneca, and Sanofi SA. Robin H. Heijmen has been a consultant for Medtronic. Jurrien M. ten Berg reported receiving grant funding from ZonMw (Dutch government) and Daichi Sankyo Company Limited. Pim A.L. Tonino received grant funding from Opsens and Biosensors International and personal fees from Medtronic PLC. Ronak Delewi has received grant funding from Abiomed Inc, Boston Scientific Corporation, Edwards Lifesciences, Sanofi SA, Meril life Science, Amgen, and Novartis AG. Niels van Royen has received research funding from Abbott, Philips, Medtronic and Biotronik, has served as a consultant for RainMed, Castor and Medtronic and received speaker fees from Abbott and Bayer.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data underlying this article will be shared upon reasonable request to the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.
Supplementary file.