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VALVULAR AND STRUCTURAL HEART DISEASES

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EDITORIAL COMMENT: Expert Article Analysis for:
Access site vascular complications in TAVR: Is this the right time?

Access site related vascular complications with third generation transcatheter heart valve systems

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Abstract

Objectives: This study examines the impact of anatomical and procedural factors on Valve Academic Research Consortium-2-defined vascular complications at the femoral access site in transcatheter aortic valve replacement (TAVR) with third generation transcatheter heart valve (THV)-systems.

Background: Randomized clinical trials reported on vascular complications with current THV-systems. However, clinical presentation and consequences of these events are not well studied.

Methods: All patients who underwent a transfemoral TAVR using an Edwards Sapien3®/Sapien3ultra® or a Medtronic Evolut-R®/Evolut-PRO® have been identified from our institutional database. Only procedures utilizing the PerClose-ProGlide® vascular closure device were included. Risk factors for vascular complications were analyzed with a logistic regression model. Preoperative and procedural data were collected. The postoperative course of patients with and without vascular complications was compared.

Results: A total of 878 patients met the inclusion criteria. Of these, 152 patients (17.3%) had an access-site related vascular complication (87 major complications, 9.9%). Sheath-to-femoral-artery-ratio (SFAR) (OR per 0.1 increase = 1.35, $p < .001$) and more than 2 vessel entries with large bore sheaths (OR = 1.76, $p = .029$) were independent risk factors for vascular complications. Female gender (OR = 1.44, $p = .07$) and two vessel entries with large bore sheaths (OR = 1.2, $p = .53$) increased the risk, although no statistical significance was shown.

Age (OR = 1.07, $p = .62$), body mass index (OR = 1.1 per 5 points, $p = .32$) and vessel wall calcification at puncture site (OR = 0.93, $p = .7$) had no influence on vascular

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; RCT, randomized clinical trial; SFAR, sheath to femoral artery ratio; TAVR, transcatheter aortic valve replacement; THV, transcatheter heart valve; VARC, Valve Academic Research Consortium; VCD, vascular closure device.

complications. Patients with vascular complications had a higher need for blood transfusion ($p < .001$) and a higher in-hospital mortality (2.6 vs. 0.4%, $p = .019$).
Conclusions: Procedural risk assessment should include SFAR calculation and consider the need for large bore sheath exchange. This might reduce the vascular trauma, lower vascular complication rates and improve the clinical outcome after TAVR.

KEYWORDS
percutaneous valve therapy, transcatheter valve implantation, vascular closure device

1 | INTRODUCTION

Vascular complications are still of concern in transfemoral transcatheter aortic valve replacement (TAVR). The majority of vascular complications arise at the large bore puncture site.[1]

Third-generation transcatheter heart valve (THV) systems are designed to lower vascular trauma, by introducing smaller sheath profiles, expandable or integrated delivery sheaths. The integrated delivery sheath, as used in the Medtronic systems, has a true low profile of a 14 French equivalent. This concept requires multiple vessel entries with large-bore sheaths as predilatation of the vessel and of the aortic valve, THV delivery and post-dilatation utilize different sheaths. The expandable sheath strategy, used by Edwards devices, presents with a true outer diameter of 22–24.5 French. This concept allows performing the whole TAVR-procedure with only one vessel entry.

Only few other studies have reported on vascular complications with third generation THV systems. The design of these studies makes their results difficult to interpret. Either only one THV system was investigated[2] or various vascular closure device (VCD) systems,[3] or different second and third generation THV systems.[4] Randomized clinical trials (RCTs) report Valve Academic Research Consortium (VARC)-2 defined major vascular complications with third-generation THV ranging from 6 to 7.9% in intermediate risk- and from 2 to 3.8% in low risk patient cohorts.[5-9] However, these studies lack to provide details of underlying mechanisms, clinical consequences and therapies of vascular complications. In previous studies focusing on vascular complications, sheath to femoral artery ratio (SFAR), vessel calcification and female gender were identified as risk factors.[1,10-12] However, those studies exclusively included early generation THV systems.[1,10,11]

We report on the rate of vascular complications and their clinical consequences using third generation THV systems. Furthermore, we sought to identify risk factors for vascular complications. This may lead to better understand the potential cause of these events.

2 | MATERIALS AND METHODS

This retrospective, single center study was conducted at the Department of Cardiovascular Surgery at the German Heart Center Munich.

All patients who underwent TAVR with a third generation THV (Edwards Sapien 3®, Sapien 3 ultra® and Medtronic Evolut R®, Evolut PRO®) were identified in our institutional TAVR database. Of these, patients with non-femoral access and utilization of a VCD other than Perclose ProGlide® were excluded (Figure 1).

Ethics committee approval was gained (118/20 S).

2.1 | Vascular access and closure

Puncture of the common femoral artery for THV access was performed following angiography from the contralateral site. We aimed for 10 mm distance to the femoral bifurcation at least. Two Perclose ProGlide® were placed in standard preclose technique. For implantation of an Edwards Sapien THV, the appropriate 14 French or 16 French eSheath® or 14 French Axela® sheath was advanced over an extra stiff wire. Utilization of the Edwards Sapien THV systems allowed a single vessel entry strategy. A Medtronic THV was implanted either using the 14 French or 16 French (for Evolut R 34 or Evolut Pro THV) InLine sheath® concept or an appropriate larger sheath. An 18 French or 20 French sheath (for Evolut R 34 or Evolut Pro THV) allowed a single vessel entry as it facilitates the THV delivery and delivery of valvuloplasty balloons if needed. Utilization of the InLine sheath® required repeated vessel entries with large bore sheaths. Per the company's guidelines an additional 14 French or 16 French (for Evolut R 34 or Evolut Pro THV) sheath was used for predilatation of the access vessel and an potential aortic valve predilatation. Postdilatation required a third insertion of the large bore sheath.

After removal of the large bore sheath over a guidewire, the puncture hole was closed in standard fashion with tying the two Perclose ProGlide® sutures using the knot pusher. Administration of protamine was to the operator's discretion.

2.2 | Endpoints

The primary endpoint was any VARC-2-defined vascular complication at the femoral access site during hospitalization. We chose potential risk factors contributing to vascular complications based on published data and clinical considerations (Table 1). Secondary endpoints included VARC-2 defined bleeding at the access site, need for blood transfusion, length of hospital stay and in-hospital mortality.

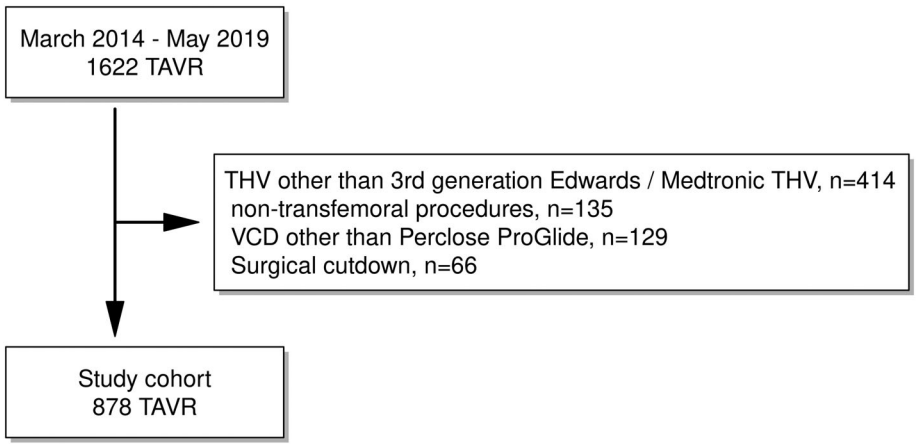

FIGURE 1 Patient selection. Figure displays the selection process resulting in a cohort of 878 patients

TABLE 1 Potential risk factors for vascular complications at the femoral access site

Potential risk factors analyzed	Potential risk factors leading to vascular complications
Vessel wall calcification at access site	Anterior and posterior vessel wall calcification may impede vascular closure device (VCD) performance.
Age	Vessel wall strength and elasticity decrease with increasing age
Gender	Vessel wall strength may differ with gender. Identified as risk factor in previous publications.
Body mass index	Larger skin to vessel distance challenges precise vessel puncture and may impede VCD performance.
Sheath-to-femoral-artery-ratio	Higher strain/trauma during sheath insertion. Identified as potential risk factor in previous publications.
Number of vessel entries	Repeated vessel entries with large-bore sheaths as required with the low-profile sheath concept may cause higher vessel trauma.

Note: Risk factors selected on the mechanism potentially leading to vascular complications.

2.3 | Data collection

Demographics, procedural details, intra-hospital course and adverse events were prospectively recorded according to the VARC-2 recommendations[13] in our dedicated TAVR database. In addition, the data were validated by reviewing operative reports, medical records and intra-procedural angiography studies.

Each procedure was categorized to one, two or more than two vessel entries with large bore sheaths reviewing the operation report. Utilized large bore sheaths allowed for SFAR calculations.

All available preoperative computerized tomography studies underwent study-specific secondary assessment: This assessment was performed by one experienced examiner, unaware of the performed procedure and patient outcome. Femoral artery diameter at access site was re-evaluated. Vessel wall calcification at the puncture site region between femoral bifurcation and cranial margin of the hip was graded as none, minimal, moderate or severe based on qualitative, visual assessment (Figure 2). Calcification-grade was determined for anterior, posterior, lateral and medial vessel wall separately.

2.4 | Statistical analysis

Statistical analysis was conducted using R statistical software language (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as mean ± *SD* or as median (interquartile range), categorical variables are expressed as percentages. Risk factor analysis was performed using a multivariable logistic regression model. Table 1 displays the variables chosen and provides the rationale why they were chosen. The results were reported as odds ratios (ORs) and 95% confidence interval (CIs). Comparison between groups was performed using either a Fisher exact test for binominal variables, *t* test for normal distributed variables and a Wilcox Rank-sum test for the remaining variables. A p value of <.05 was considered as significant.

3 | RESULTS

3.1 | Baseline and procedural characteristics

Between March 2014 and April 2019, 878 patients met the inclusion criteria (Figure 1). Table 2 displays the demographic and procedural data of the total cohort. Overall, 418 Evolut R®, 41 Evolut PRO®, 405 Sapien 3® and 14 Sapien 3 ultra® were implanted (Table 3). Preoperative computerized tomography studies were available for secondary assessment in 834 patients (95%).

3.2 | Incidence and type of vascular complications

In total, 158 VARC-2 defined access-related vascular complications (major n = 87, 9.9%; minor n = 71, 8.1%) occurred in 152 (17.3%)

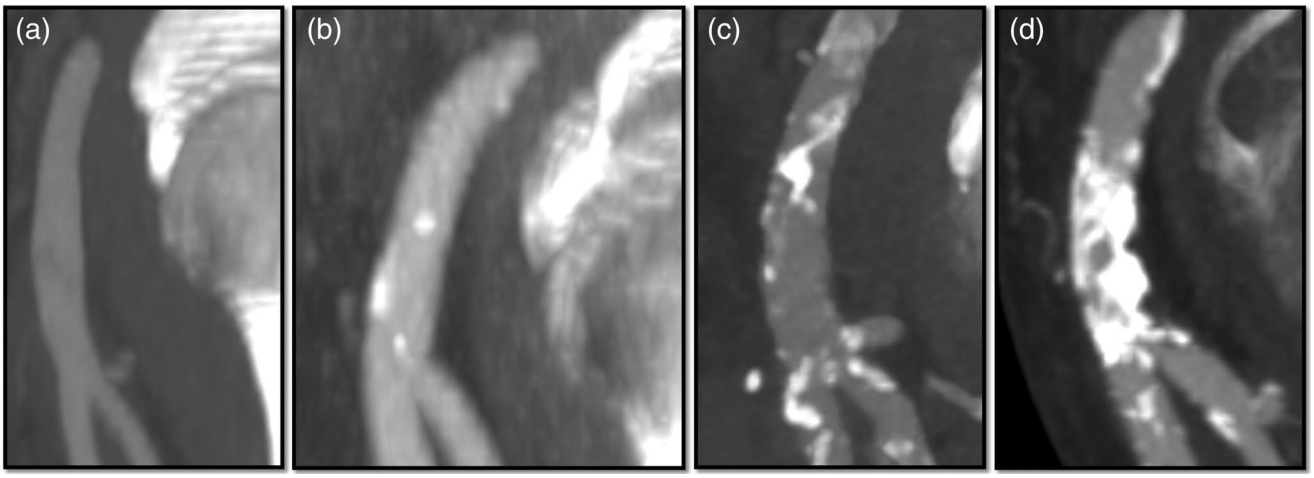

FIGURE 2 Assessment of vessel wall calcification. Visual, qualitative assessment of vessel wall calcification of the common femoral artery from bifurcation to the top of the femoral head. Multiplanar reconstruction of the computerized tomography displays calcification grades of none (a), mild (b), moderate (c) and (d). Revision of axial slides determined anterior, posterior, medial or lateral calcium localization

patients. Table 4 displays details on access-related vascular complications and their consecutive treatment. Of the 152 patients with a vascular complication, 90 patients (59.2%) also met the VARC-2-criteria for a access site bleeding complication. Specifically within the 87 major vascular complications, intraprocedural bleeding for VCD failure (70.1%) and postprocedural hematoma (6.9%) accounted for the majority of the events. Treatment of those events was conservative (pressure compression) in 49.2%, surgical in 29.5% and interventional in 21.3%.

In 11 patients a life-threatening bleeding according to VARC 2 occurred.

3.3 | Impact of vessel wall calcifications

Table 5 displays the distribution of vessel wall calcification. Only 1% of the patients had severe calcifications at the anterior and 7% at the posterior vessel wall. Of nine patients with severe anterior wall calcifications, two (22%) had a major vascular complication. Both patients had severe posterior wall calcifications as well. Of 62 patients with severe posterior wall calcification, eight (12.9%) experienced a major vascular complication.

3.4 | Risk factor for vascular complications

The multivariable logistic regression model (Figure 3) indicates that SFAR (OR 1.35, $p < .001$) and more than 2 vessel entries (OR 1.76, $p = .029$) were independent risk factors of access-related vascular complications. Female gender (OR 1.44, $p = .07$) and two vessel entries increased the risk for a vascular complication although these effects were not statistically significant. Vessel wall calcification (classified as moderate or severe), BMI and age had only a no significant effect on the rate of vascular complications.

3.5 | Clinical consequence of vascular complications

In patients with an access-related vascular complication length of stay was longer ($p = .013$) and wound infections occurred more often ($p < .001$). A transfusion was required in 67.1% of the patients with a vascular complication versus 25.8% in the patients without a vascular complication ($p < .001$).

Intra-hospital mortality was 0.8% for the total cohort. Patients with a vascular complication had a significantly increased intra-hospital mortality (2.6% vs. 0.4, $p = .019$).

4 | DISCUSSION

In the current study, 9.9% of patients undergoing a transfemoral TAVR experienced a major vascular complication. Recent RCTs on intermediate risk patients report similar rates of 6–8%.[5,8,9] However, patients included in RCTs are highly selected and reported complication rates cannot be transferred to an all-comer population as in our study. Bleeding for VCD failure was the most common cause for major vascular complications.

Using a risk factor analysis, we aimed to identify factors associated with vascular complications. The two major risk factors were higher SFAR and more than two vessel entries, both procedure-related risk factors. SFAR has been identified as an independent risk factor for vascular complications in other studies including mainly first generation THV systems.[1,10,11] We are the first to show that

TABLE 2 Baseline characteristics, procedural details and clinical outcome of the total study cohort and comparison of patients with and without access-related vascular complication

	Total cohort	No vascular complication	Vascular complication	*p* value
Patients	878	726	152	
Age (years)	80 ± 7.5	79.9 ± 7.4	80.3 ± 7.5	.48
Gender (female)	424 (48%)	332 (46%)	92 (61%)	<.001
Height (cm)	167.7 ± 9.2	168.2 ± 9.3	165.6 ± 8.2	<.001
Weight (kg)	75.4 ± 15.55	75.7 ± 15.1	74.0 ± 17.8	.053
Coronary artery disease	467 (53.3%)	375 (51.8%)	92 (60.5%)	.06
Peripheral artery disease	102 (11.6%)	77 (10.6%)	25 (16.4%)	.051
Cerebrovascular disease	52 (6%)	38 (5.3%)	14 (9.2%)	.087
Previous stroke	85 (10%)	75 (10%)	10 (7%)	.18
COPD	114 (13%)	89 (12%)	25 (17%)	.18
Creatinin (mg dl)	1.3 ± 0.8	1.3 ± 0.8	1.3 ± 0.7	.11
GFR (ml/min)	59.4 ± 23.3	60.4 ± 22.9	54.6 ± 24.5	<.001
Pro-BNP ng/ml	4,620 ± 6,997.3	4,413.4 ± 6,930	5,661.5 ± 7,274.2	.005
LVEF >50%	585 (66.8%)	491 (67.8%)	94 (61.8%)	.18
LVEF 35–50%	192 (21.9%)	152 (21%)	40 (26.3%)	
LVEF <35%	98 (11.2%)	80 (11%)	18 (11.8%)	
EOA (cm)	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2	.82
Aortic valve max. gradient (mmHg)	65.7 ± 25.1	66.5 ± 25.4	62 ± 23.7	.049
Aortic valve mean gradient (mmHg)	40.7 ± 16.5	41.1 ± 16.8	38.9 ± 15.5	.13
Aortic annulus diameter (mm)	23.9 ± 2.6	24 ± 2.6	23.6 ± 2.6	.1
STS PROM	4.2 ± 3.8	4.2 ± 3.7	4.1 ± 4.4	.19
EuroScore 2	5.7 ± 6.2	5.6 ± 5.8	6.1 ± 7.8	.89
EuroScore, logistic	16.9 ± 12.4	16.8 ± 12.1	17.1 ± 14.1	.78
Hb preop	12.4 ± 1.81	12.56 ± 1.75	11.65 ± 1.91	<.001
HK preop	36.95 ± 4.99	37.37 ± 4.77	34.91 ± 5.52	<.001
Hb discharge	11.1 ± 1.41	11.2 ± 1.43	10.65 ± 1.26	<.001
HK discharge	33.28 ± 4.11	33.53 ± 4.15	32.09 ± 3.73	<.001
PRBCS are 0	589 (67.2%)	537 (74.2%)	52 (34.2%)	<.001
PRBCS are 1–2	176 (20.1%)	127 (17.5%)	49 (32.2%)	
PRBCS are >2	111 (12.7%)	60 (8.3%)	51 (33.6%)	
Length of stay	7 (5–9)	7 (5–8)	7 (5.5–10)	.013
Inhospital death	7 (0.8%)	3 (0.4%)	4 (2.6%)	.019
Wound infection	10 (1.1%)	1 (0.1%)	9 (5.9%)	<.001
Number of vascular access: 1	519 (59.1%)	426 (58.7%)	93 (61.2%)	.87
Number of vascular access: 2	179 (20.4%)	155 (21.3%)	24 (15.8%)	
Number of vascular access: >2	180 (20.5%)	145 (20%)	35 (23%)	
Largest sheath OD mm	7.1 ± 0.8	7.1 ± 0.8	7.2 ± 0.8	.46
SFAR	0.91 ± 0.17	0.90 ± 0.16	0.97 ± 0.18	<.001

Abbreviations: COPD, chronic obstructive pulmonary disease; EOA, effective orifice area; Hb, hemoglobin; Hk, hematocrit; LVEF, left ventricular ejection fraction; OD, outer diameter; PRBCS, packed red blood cell transfusion; SFAR, sheath-to-femoral artery-ratio; STS PROM, Society of Thoracic Surgery predicted risk of mortality score.

exchanges of large bore sheaths may also increase access-related vascular complications.

The specific design of third generation THV systems intends to reduce vessel trauma by two different mechanisms. The low-profile sheath concept from Medtronic, for example, the Medtronic® InLine sheath utilizes 14–16 French sheaths. This concept might offer a lower SFAR. However, exchange of large bore sheaths with multiple vessel entries are required to perform pre- and/or

postdilatation and THV implantation, respectively. In contrast, the expandable high-profile sheath concept from Edwards, for example, the Edwards Lifescience® eSheath requires just one vessel entry with a large bore sheath. A potential drawback of this strategy is the larger 22–24.5 French outer diameter of the sheath maybe leading to higher SFAR. Our study confirms that both technologies, either reduction in sheath diameter or a single vessel entry are reasonable strategies. To find out if one strategy is superior to the other a different study design would be required.

To our surprise, vessel wall calcification at access site was no risk factor for vascular complications. In previous studies, access vessel calcification was associated with vascular complications.[11,12] Anterior wall calcification has a stronger impact on vascular complication than

TABLE 3 Transcatheter heart valve selection (type and size)

	Valve size				
	20	**23**	**26**	**29**	**34**
Evolut R/PRO, *n*		48	158	184	69
Sapien 3/ultra, *n*	2	148	167	102	

TABLE 4 Major and minor vascular complications with underlying mechanism and treatment at the femoral access site

			Surgical	Interventional	Thrombin-injection	Conservative
Major vascular complications	Events, *n*	87	23 (26%)	27 (31%)	0 (0%)	37 (34%)
	Bleeding (intraprocedural)	61	18	13	0	30
	Bleeding (postproc. hematoma)	6	0	1	0	5
	Vessel dissection	9	2	7	0	0
	Vessel stenosis/occlusion	10	3	6	0	1
	False aneurysm	1	0	0	0	1
Minor vascular complications	Events, *n*	71	15 (21%)	20 (28%)	6 (8%)	30 (42%)
	Bleeding (intraprocedural)	16	9	3	0	4
	Bleeding (postproc. hematoma)	7	0	0	0	7
	Vessel dissection	10	0	3	0	7
	Vessel stenosis/occlusion	19	6	12	0	1
	False aneurysm	19	0	2	6	11

TABLE 5 Vessel wall calcification graded none, mild, moderate and severe

		Posterior wall calcification		
		None/mild	**Moderate**	**Severe**
Anterior wall calcification	**None/mild**	56%	30%	4%
	Moderate	1%	6%	2%
	Severe	0%	0%	1%

Note: Localization specified to anterior and posterior vessel wall.

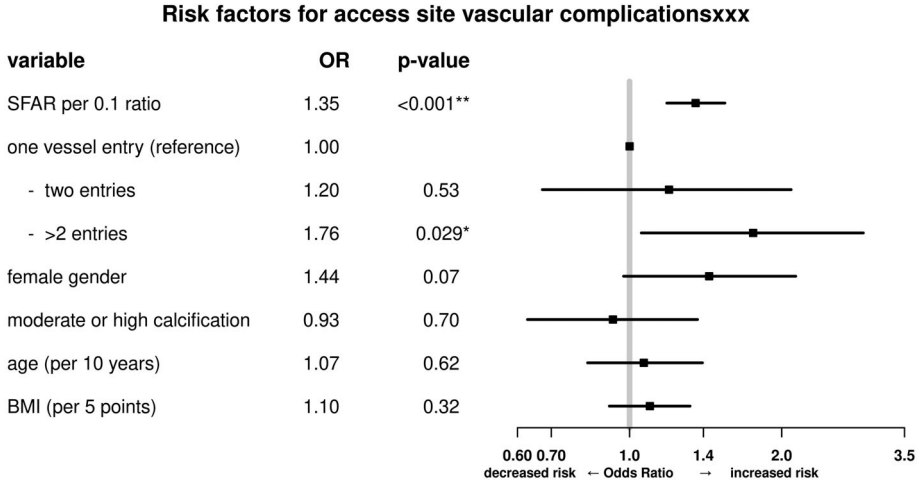

FIGURE 3 Risk factor analysis for access related vascular complications. A multivariable logistic regression model indicates that increasing SFAR and repeated vascular access are risk factors for access site related vascular complications in transfemoral TAVR. SFAR, sheath-to-femoral artery-ratio; TAVR, transcatheter aortic valve replacement

posterior wall calcification.[12] In the present study, only few patients had severe calcifications, because these patients usually underwent surgical cut-down. Although there were relevant vascular complications in patients with severe calcification, the number of patients was too small for statistical power. Moderate vessel wall calcification seems to allow a safe transfemoral TAVR procedure.

It remains unclear, whether female gender per se is a risk factor for vascular complications. Probably, female gender is associated with smaller vessel diameter, resulting in a less favorable SFAR. This may be the main reason why previous studies found female gender as a risk factor for vascular complication.[1,10] In our analysis, female gender was associated with more vascular complications independent from SFAR. However, this effect did not reach statistical significance.

Consistent with previous findings,[14] BMI did not influence the occurrence of vascular complications. Despite the more challenging vessel puncture due to a larger skin-to-vessel distance and a potentially impeded VCD performance, vascular complications were not increased in our cohort.

Also age, suspicious to impede vessel wall elasticity and VCD performance, had no influence on vascular complications in our study.

The clinical consequence of access site vascular complications are highly relevant: Patients with an access-related vascular complication had almost a threefold higher intra-hospital mortality. Patients required more red blood cells transfusions and had a longer hospital stay.

We focused our analysis on the Perclose ProGlide®, as suture-mediated closure is the most commonly used technique to seal the large bore arterial puncture site in TAVR procedures.

The study-specific re-evaluation of the computerized tomography images on vessel diameters and calcification pattern improved the validity of the two important factors "SFAR" and "calcification."

Besides the established VCD systems, dedicated large bore VCD systems have been introduced.

First studies report low vascular complication rates for novel vascular closure devices such as the MANTA (Teleflex, Morrisville, NC) and the InClosure VCD (InSeal Medical, Caesarea, Israel).[15,16] Further studies need to determine, whether the novel vascular closure device systems can lower vascular complication rates achieved with the suture mediated devices.

5 | LIMITATIONS

The study is limited to our single-center experience and the retrospective study design. The data have not been reviewed by an independent adjudication committee. Due to the low number of patients with severe calcification, we cannot determine the influence of severe calcification on vascular complications.

6 | CONCLUSION

Access-related major vascular complications are below 10% and have clinically highly relevant consequences for blood transfusion requirements, access site infection, hospital stay and in hospital mortality. High SFAR and repeated vessel entries with large bore sheaths are risk factors for access-related vascular complications. Age, obesity and vessel wall calcification up to a moderate degree do not increase the risk for access-related vascular complications.

Procedural risk assessment should include SFAR calculation and consider the need for large bore sheath exchange. This might reduce the vascular trauma, lower vascular complication rates and improve the clinical outcome after TAVR.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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