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Frequency, Impact, and Predictors of Access Complications With Plug-Based Large-Bore Arteriotomy Closure - A Patient-Level Meta-Analysis

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ABSTRACT

Background/purpose: The MANTA is a dedicated plug-based large-bore vascular closure device (VCD) providing safe hemostasis in most patients, but data on the clinical impact and mechanisms of MANTA related complications are limited. This study sought to determine the frequency, impact and predictors of MANTA-related access complications.

Methods/materials: This patient-level meta-analysis included data from 2 medical device approval studies and 1 post-approval registry. The primary endpoint was the composite of major and minor access complications. Technical success was defined as hemostasis with MANTA closure device without need for vascular surgery or stenting.

Results: Eight hundred ninety-one patients (mean age 80) underwent transcatheter aortic valve replacement ($n = 814$), endovascular aortic repair ($n = 71$), balloon aortic valvuloplasty ($n = 4$) or mechanical circulatory support ($n = 2$). Technical success was 96.4% and median time to hemostasis was 31 (interquartile range: 17–76) seconds. The primary endpoint occurred 9.1% and bailout vascular surgery or stenting was necessary in 32 patients (3.6%). Female gender (OR: 2.63, CI: 1.46–4.73, $p = 0.001$), left femoral access (OR: 2.18, CI: 1.17–4.06, $p = 0.015$) and unfavorable arteriotomy phenotype (combination of a small femoral artery diameter with a deep arteriotomy; OR 2.27: 1.26–4.10, $p = 0.006$) independently predicted access complications. Access complications most often consisted of vessel dissection, stenosis or occlusion and predominantly occurred in patients with an unfavorable arteriotomy phenotype.

Conclusions: Large-bore arteriotomy closure with MANTA VCD provided fast and safe hemostasis with an acceptable complication rate. Refined procedure planning and risk-stratification may further improve MANTA VCD performance.

1. Introduction

Modern catheter-based techniques such as transcatheter aortic valve replacement (TAVR), endovascular abdominal aneurysm repair (EVAR) and mechanical circulatory support systems offer minimally invasive treatment strategies for complex cardiovascular disease but require large-bore femoral artery sheath insertion and removal. Failure to achieve succesful arteriotomy closure directly impacts perioperative outcomes including length of stay, quality of life and mortality [1]. Most experience with percutaneous large bore arteriotomy closure are accrued with suture based closure but is associated with a 10–20% vascular complication rate [2,3]. The MANTA vascular closure device (VCD; Teleflex Inc., Pennsylvania, United States of America) is a collagen-based technology dedicated for large-bore arteriotomy closure with established safety and efficacy [4–6]. Still, MANTA closure failure may occur. Not much is known about predictors for MANTA closure failure and associated access complications. The aim of this patient level meta-analysis was to gain more granularity into the frequency, impact and predictors of MANTA related access complications.

Abbreviations: AFAP, arteriotomy depth femoral artery diameter phenotype; MARVEL, MAnta Registry for Vascular Large-borE Closure; MLD, minimal lumen diameter; VARC-2, Valve Academic Research Consortium-2; VCD, vascular closure device.

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2. Materials and methods

2.1. Patients

This patient-level pooled analysis included 891 patients who underwent TAVR ($n = 814$), EVAR ($n = 71$) or other percutaneous interventions ($n = 6$) with large-bore catheter sizes (14-F to 20-F inner diameter sheaths or devices) and planned access closure using the MANTA VCD. Patients were enrolled in 2 multicenter, prospective, single arm medical device approval studies (the Conformite Européene [CE] mark study, $n = 50$, and the Investigational Device Exemption SAFE-MANTA Pivotal Study, $n = 341$) and a third multicenter, prospective post-approval study (the MAnta Registry for Vascular Large-borE CLosure [MARVEL] registry, $n = 500$) [4–6].

Study characteristics and details of in- and exclusion criteria are presented in the supplementary [7]. Exclusion criteria were most stringent in SAFE-MANTA followed by the CE-mark study while the post-approval MARVEL registry was more liberal and applied only relative exclusion criteria that were left at the discretion of the operator. Morbid obesity (body mass index >40 kg/m^2) and excessive calcification and/or tortuosity of the iliofemoral artery precluding safe access in the opinion of the operator were consistent exclusion criteria in the three trials. Important additional exclusion criteria in the SAFE MANTA trial were severely reduced ejection fraction and end-stage renal disease. Procedures were performed by 71 operators at 28 investigational sites across Canada, Europe and the United States between July 2015 and August 2019. The analysis included also the 78 Roll-in cases (i.e. first or second time operator use of the MANTA VCD) from SAFE-MANTA. Conceivably, the patient population in this pooled analysis mirrored the clinical reality of large-bore arteriotomy management with the MANTA VCD by operators at various levels of experience. All studies complied with the Declaration of Helsinki and were approved by the Institutional Review Board of each participating center. All patients provided written informed consent before enrollment.

2.2. Device description

A description of the MANTA VCD and deployment procedure were described in detail elsewhere [4,5]. In brief, the device consists of an intravascular, low profile, resorbable polymer anchor connected with a suture attached to an extravascular hemostatic bovine collagen pad. The arteriotomy is sandwiched between the intravascular anchor and the extravascular collagen pad providing both mechanical and biological hemostasis. The 14-F MANTA device is indicated for closure of 10- to 14-F sheaths/devices (maximum 18-F outer diameter) and the 18-F MANTA is used for 15- to 20-F sheaths/devices (maximum 25-F outer diameter).

2.3. Procedures

Pre-procedure imaging consisted of multislice computed tomography of the peripheral arteries to determine any significant vascular pathology, the minimal lumen diameter (MLD) of the iliofemoral trajectory and the planned target access site (left or right common femoral artery). Chronic anticoagulation therapy was interrupted prior to all procedures. Ultrasound guided arterial puncture was recommended but not mandatory. Prior to arteriotomy closure, target systolic blood pressure was <180 mmHg and the recommended ACT was <250 s. Protamine was administered at the discretion of the operator. Angiographic confirmation of complete hemostasis was required following deployment of the MANTA device. In all cases, one MANTA VCD was used for the target access site; any contralateral or ipsilateral second access site was closed using standard arteriotomy closure techniques.

2.4. Iliofemoral data

Arteriotomy depth was measured using the dedicated MANTA depth locator provided in the MANTA kit and featured the distance from skin entry to the arteriotomy, which was affected by the puncture angulation (in principle 45°; Online Fig. 1). A deep arteriotomy (i.e. covered by a long trajectory of subcutaneous tissues) and small femoral artery diameter were suspect for a higher risk for VCD failure and access complications. We looked at different phenotypes based on arteriotomy depth and femoral artery diameter (AFAP) as follows:

(i) AFAP-1 = Shallow arteriotomy and large femoral diameter: depth < 40 mm and diameter ≥ 8 mm,
(ii) AFAP-2 = Deep arteriotomy and large femoral diameter: depth ≥ 40 mm and diameter ≥ 8 mm; or shallow arteriotomy and small femoral diameter: depth < 40 mm and diameter < 8 mm,
(iii) AFAP-3 = Deep arteriotomy and small femoral diameter: depth ≥ 40 mm and diameter < 8 mm.

Arteriotomy-depth and femoral artery diameter cutoff values were derived from the respective median values of the entire cohort. Since patients with severe vessel tortuosity and calcification were excluded in the CE-mark and SAFE-MANTA trials, these variables were not included in the current analysis.

2.5. Clinical outcomes

Time to hemostasis was defined as the elapsed time between MANTA deployment and the first observed arterial hemostasis (no or minimal subcutaneous oozing and the absence of expanding or developing hematoma). MANTA technical success was defined as hemostasis without the use of bailout surgery or endovascular stenting. The primary endpoint was the composite of MANTA related minor and major access site complications of which definitions were adapted from the Valve Academic Research Consortium-2 (VARC-2) criteria. MANTA related life-threatening and major bleeding definitions were complied with VARC-2 criteria if related to the target access site. Total complication rates were calculated using hierarchical priority on a per-subject basis with the most relevant event/intervention included in the analyses. In all studies, clinical follow-up was planned between 30- and 60 days after the procedure. An independent clinical research organization overlooked study conduction and monitoring in all 3 individual trials. All vascular- and bleeding complications were adjudicated by independent clinical event committees.

2.6. Statistical analysis

A unique database was constructed for all patient-level data from the 3 trials; 1.5% of data were missing. Categorical variables were presented as frequencies and percentages and were compared with the Chi-square test or Fisher exact-test. Normal and skewed continuous variables were presented as means (standard deviation) and medians (interquartile range), respectively. Continuous variables were compared using the Student t-test or Mann Whitney *U* test when appropriate.

To determine predictors of any MANTA related access site complication, we entered the variables listed in Tables 1 and 2 that were of clinical interest and/or exhibiting $p < 0.05$ in the univariable analyses into a multivariable logistic regression analysis, except variables measuring the same phenomenon of which those with less statistical significance was excluded. As such, femoral diameter and arteriotomy depth were excluded in favor of AFAP-3 (versus AFAP-1 or 2). Two sided *p*-values <0.05 were considered statistically significant. All statistical analyses were performed using Statistical Package for Social Science for Windows version 21. Two sided p-values <0.05 were considered statistically significant.

Table 1
Patient characteristics for patients with and without access complications.

	Total	No access complication	Access complication	p-Value
Characteristic	$N = 891$	$N = 810$	N = 81	
Age, mean (SD), y	80 (8)	80 (8)	82 (6)	0.006
Female gender	364 (41)	316 (39)	48 (59)	<0.001
Body mass index, median (IQR), kg/m^2	27 (24–30)	27 (25–30)	26 (24–30)	0.065
Peripheral vascular disease	91 (10)	79 (10)	12 (15)	0.15
Previous coronary artery bypass graft	126 (14)	119 (15)	7 (9)	0.14
Previous percutaneous coronary intervention	263 (30)	235 (29)	28 (35)	0.30
Previous cerebrovascular event	94 (11)	83 (10)	11 (14)	0.35
Permanent pacemaker	87 (10)	74 (9)	13 (16)	0.050
Glomerular filtration rate < 60 mL/min	453 (51)	406 (50)	47 (59)	0.14
Society of Thoracic Surgeons' score, median (IQR), %	3.2 (2.1–4.9)	3.1 (2.1–4.7)	4.4 (2.5–6.4)	0.009
Oral anticoagulant	199 (22)	180 (22)	19 (24)	0.80
New oral anticoagulant	87 (10)	79 (10)	8 (10)	0.97

3. Results

The mean age of the entire population was 80 years and the median Society of Thoracic Surgeons (STS) predicted risk of mortality was 3.2 (IQR: 2.1–4.9) percent. Technical success was achieved in 96.4% of the patients and the median time to hemostasis was 31 (IQR: 17–76) seconds. The distribution of hemostasis times is shown in the supplementary [7].

The baseline patient characteristics and procedural details of the total population and of patients with and without MANTA related minor or major access complications are presented in Tables 1 and 2, respectively. Access complications, the primary endpoint of this study, occurred in 9.1% of the patients. Patients with access complications were older (82 vs. 80 years, $p = 0.006$), more often female (59 vs. 39%, $p < 0.001$) and were at higher operative risk (STS score 4.4 vs. 3.1%, $p = 0.009$). Also, patients with access complications were more often treated via the left femoral route (33 vs. 18%, $p = 0.001$), had a smaller mean femoral diameter (7.57 vs. 7.97 mm, $p = 0.028$) and more frequently had AFAP-3 (39 vs. 24%, $p = 0.006$).

Procedure duration (93 vs. 63 min, $p < 0.001$) and length of hospital stay (3 vs. 2 days, $p = 0.038$) were significantly longer in patients with access complications as compared to those without.

3.1. Access complications and clinical impact

Access complications and details on additional treatment requirements are summarized in Table 3; a case-level overview is shown in the supplementary [7]. Overall, 3.6% required surgical bailout or a covered stent for a major (2.9%) or minor (0.7%) access site complication.

A major access complication occurred in 39 patients (4.4%) and consisted of a flow-limiting dissection, stenosis or occlusion in 22 patients, incomplete arteriotomy closure in 15 and a pseudo-aneurysm in 2. Surgery and/or stenting was required in 26 patients (2.9%). All complications were diagnosed ≤1 day after the procedure except 1 patient who suffered incomplete arteriotomy closure complicated by retroperitoneal hemorrhage that was identified on day 6.

A minor access complication occurred in 42 patients (4.7%) and consisted of a pseudo-aneurysm ($n = 16$), incomplete arteriotomy closure ($n = 13$), dissection or stenosis ($n = 12$) or transient nerve injury (n = 1). Additional vascular surgery or stenting was performed in 6 patients (0.7%). A total of 38 cases were diagnosed ≤1 day after the procedure and 4 were identified post- discharge on day 27, 34, 41 and 57 post-procedure all consisting of a pseudo-aneurysm for which no additional treatment was required.

Overall, access complications were associated with life-threatening bleeding in 4 patients (0.4%) and major bleeding in 15 patients (1.7%). A total of 13 deaths (1.5%) occurred at a median of 13 (IQR 2-24) days

Table 2
Procedural characteristics for patients with and without access complications.

	Total	No access complication	Access complication	p-value
Characteristic	N = 891	N = 810	N = 81	
Vascular access				
Right femoral artery[a]	722 (81)	667 (82)	55 (68)	0.002
Left femoral artery[a]	170 (19)	143 (18)	27 (33)	0.001
14-Fr MANTA vascular closure device[b]	90 (10)	79 (10)	11 (14)	0.50
18-Fr MANTA vascular closure device[b]	799 (90)	729 (90)	70 (86)	
Femoral diameter, mean (SD), mm	7.94 (1.54)	7.97 (1.53)	7.57 (1.67)	0.028
Arteriotomy-depth, mean (SD), mm	38 (12)	38 (12)	40 (12)	0.18
Arteriotomy-depth/femoral-diameter phenotype[c]				
AFAP-1	231 (27)	219 (28)	12 (16)	0.006
AFAP-2	417 (48)	384 (49)	33 (45)	
AFAP-3	214 (25)	185 (24)	29 (39)	
Type of procedure				
Transcatheter aortic valve replacement	814 (91)	740 (91)	74 (91)	1.0
Edwards Sapien3/Sapien3 ULTRA	443 (50)	402 (50)	41 (51)	0.87
Medtronic Evolut PRO	137 (15)	119 (15)	18 (22)	0.073
Medtronic Evolut R	127 (15)	118 (15)	9 (11)	0.35
Medtronic CoreValve System	2 (<1%)	2 (0.3)	0	1.0
Symetis Accurate Neo	72 (9)	66 (9)	6 (8)	0.72
Abbott Portico	13 (2)	13 (2)	0	0.63
Boston Scientific Lotus	9 (1)	9 (1)	0	1.0
New Valve Technology Allegra	6 (1)	6 (1)	0	1.0
Direct Flow Medical	5 (1)	5 (1)	0	1.0
Endovascular aortic repair	71 (8)	65 (8)	6 (7)	0.85
Trivascular Ovation	43 (5)	39 (5)	4 (5)	1.0
Cook Zenith Fenestrated	6 (1)	5 (1)	1 (1)	0.45
Cook Zenith Alpha	2 (0.2)	1 (0.1)	0	1.0
Cook Gianturco	1 (0.1)	1 (0.1)	0	1.0
Gore Excluder C3	11 (1)	11 (1)	0	0.61
Medtronic Endurant II	3 (0.3)	3 (0.4)	0	1.0
Endologix	4 (1)	4 (1)	0	1.0
Other procedure	6 (1)	5 (1)	1 (1)	0.44
Balloon aortic valvuloplasty	4 (0.4)	3 (0.4)	1 (1)	1.0
High risk PCI with mechanical circulatory support[d]	2 (0.2)	2 (0.3)	0	1.0
Vascular closure				
Activated clotting time before closure, median (IQR), *sec*	175 (142–217)	175 (142–217)	176 (142–212)	0.71
Systolic blood pressure before closure, mean (SD), mmHg	132 (23)	131 (23)	134 (24)	0.41
Protamine used before closure	592 (66)	539 (67)	53 (65)	0.84
Procedure duration, median (IQR), min	65 (48–87)	63 (46–83)	93 (66–125)	<0.001
Length of stay, median (IQR), days	2 (1–5)	2 (1–5)	3 (2–7)	0.038

Abbreviations: AFAP, arteriotomy-depth/artery-diameter phenotype; PCI, percutaneous coronary intervention.

[a] One patient who underwent endovascular aortic repair had access via both right and left femoral artery.

[b] For 2 MANTA implantations the F size was unavailable.

[c] AFAP data were missing in 29 patients (3%).

[d] Heartmate in one patient and Impella in another patient.

Table 3
Access complications and management.

	Access complications		
	Minor	Major	All
	$n = 42$ (4.4%)[a]	$n = 39$ (4.7%)[a]	$n = 81$ (9.1%)[a]
Type of vascular injury			
Incomplete arteriotomy closure	13 (1.5)	15 (1.7)	28 (3.1)
Dissection	9 (1.0)	3 (0.3)	12 (1.3)
Stenosis	3 (0.3)	6 (0.7)	9 (1.0)
Occlusion	0	13 (1.5)	13 (1.5)
Pseudo-aneurysm	16 (1.8)	2 (0.2)	18 (2.0)
Transient nerve injury	1 (0.1)	0	1 (0.1)
Treatment			
Surgical repair	2 (0.2)	18 (2.0)	20 (2.2)
Stenting	4 (0.4)	8 (0.9)	12 (1.3)
Prolonged balloon inflation	5 (0.5)	7 (0.8)	12 (1.3)
None/manual compression	26 (2.9)	5 (0.5)	31 (3.5)
Percutaneous injection[b]	5 (0.5)	1 (0.1)	6 (0.7)
Bleeding complications			
Life-threatening or disabling	0	4 (0.4)	4 (0.4)
Major	0	15 (1.7)	15 (1.7)

[a] Data are presented as n (%, out of a total of 891 patients).
[b] All patients underwent thrombin or lidocaine injection, except one patient who onderwent ethanol injection in the inferior epigastric artery.

after the procedure of which one (0.1%) was attributable to the MANTA VCD. Details of other causes of death are presented in the supplementary [7].

3.2. Predictors and association with vascular injury type

Univariable and multivariable logistic regression analyses for the predictors of access complications are presented in Table 4. In descending order of the magnitude of the odds ratio, independent predictors were female gender (OR: 2.63, CI: 1.46–4.73, $p = 0.001$), AFAP-3 (OR 2.27: 1.26–4.10, $p = 0.006$) and left femoral access (OR: 2.18, CI: 1.17–4.06, $p = 0.015$). Of note, Roll-in cases were not associated with access complications.

The association between AFAP and the type of vascular injury is presented in Fig. 1. From AFAP-1 to AFAP-2 and 3, there was a gradual increase in occurrence of any type of vascular injury except for injury caused by dissection, stenosis or occlusion which occurred significantly more often in patients with AFAP-3 as compared to patients with AFAP-1 or 2.

4. Discussion

The main findings of this patient-level meta-analysis encompassing 891 elderly patients at intermediate surgical risk undergoing plug-based large-bore arteriotomy closure are as follows. First, technical success was 96.4% and median time to hemostasis was 31 s. Major access complications occurred in 4.4% of the patients and minor complications in 4.7%. Second, access complications were associated with acceptable clinical impact based upon an associated low rate of life-threatening bleeding (0.4%), major bleeding (1.7%), and unplanned vascular surgery or stenting (3.6%). Moreover, death attributable to access complications was rare and occurred in 0.1%. Third, independent predictors of access complication were female gender, left femoral access and the combination of a small femoral artery diameter with a deep arteriotomy (AFAP-3). Patients with AFAP-3 were specifically at higher risk for vascular dissection, stenosis and/or occlusion. Operator experience was not associated with access complications.

The herein reported technical success rate - defined as successful hemostasis with the MANTA VCD without need for additional vascular surgery or stenting – of 96.4% is noteworthy in the context of this elderly population at intermediate surgical risk undergoing various large-bore interventions performed by operators at different levels of experience with the MANTA VCD. However, these results need interpretation from the perspective that 38% of enrolled patients stem from the SAFE-MANTA trial in which strict eligibility criteria were used. Also, excessive iliofemoral pathology and morbid obesity were exclusion criteria in the CE-mark and MARVEL registry and therefore study results cannot be extrapolated to patients with these comorbidities.

The absence of a definite learning-curve effect was reassuring particularly when considering that Roll-in cases as a group also had a higher median STS score as compared to patients not labelled as a Roll-in case (3.8 vs. 3.1%, $p = 0.015$; supplementary [7]). Moriyama et al. [8] performed a more comprehensive analysis of learning curve effects in a smaller sample size and also found no relationship with operator experience. The ease of use of the device, rapid hemostasis and absence of a learning curve compares favorably to conventional suture-based technologies.

Frequency of MANTA related major access complications was 4.4% in this study. In a sub-group of 580 patients undergoing TAVR with the two most commonly used valve-platforms today (Sapien S3/Ultra or Evolut PRO), the rate of major access complications was 5.2% [7] which corroborates smaller sized series that found major complications ranging from 2.0 to 9.3% [9,10]. In the propensity matched CONTROL study, suture-mediated closure with the Prostar XL and ProGlide device were associated with major complications in 7.4 and 1.9%, respectively, with the latter device being associated with a superior risk profile [2].

Table 4
Univariable and multivariable logistic regression analyses for associations with access complications.

	Univariable regression		Multivariable regression	
	Odds ratio (95% CI)	*p*-Value	Odds ratio (95% CI)	p-Value
Patient-related variables				
Age, per year increase	1.05 (1.02–1.09)	0.006	1.03 (0.98–1.08)	0.23
Female gender	2.27 (1.43–3.62)	0.001	2.63 (1.46–4.73)	0.001
Body mass index, per kg/m^2 increase	0.95 (0.90–1.00)	0.072	0.96 (0.90–1.03)	0.24
Peripheral vascular disease	1.61 (0.84–3.10)	0.16	1.38 (0.57–3.31)	0.47
Society of Thoracic Surgeons' score, per % increase	1.09 (1.01–1.18)	0.031	1.05 (0.96–1.16)	0.31
Arteriotomy depth, per mm increase	1.01 (0.99–1.03)	0.23	*na*[a]	*na*[a]
Femoral diameter, per mm increase	0.84 (0.72–0.99)	0.030	*na*[a]	*na*[a]
AFAP-3	2.10 (1.28–3.45)	0.003	2.27 (1.26–4.10)	0.006
Procedure-related variables				
Roll-in case	1.19 (0.57–2.47)	0.64	1.81 (0.76–4.31)	0.18
Left femoral access	2.33 (1.42–3.83)	0.001	2.18 (1.17–4.06)	0.015

Abbreviations: AFAP-3, arteriotomy-depth/artery-diameter phenotype 3 (i.e. deep arteriotomy and small femoral diameter).
[a] Arteriotomy depth and femoral diameter were excluded from multivariable regression analyses since they measure partly the same phenomenon as AFAP-3.

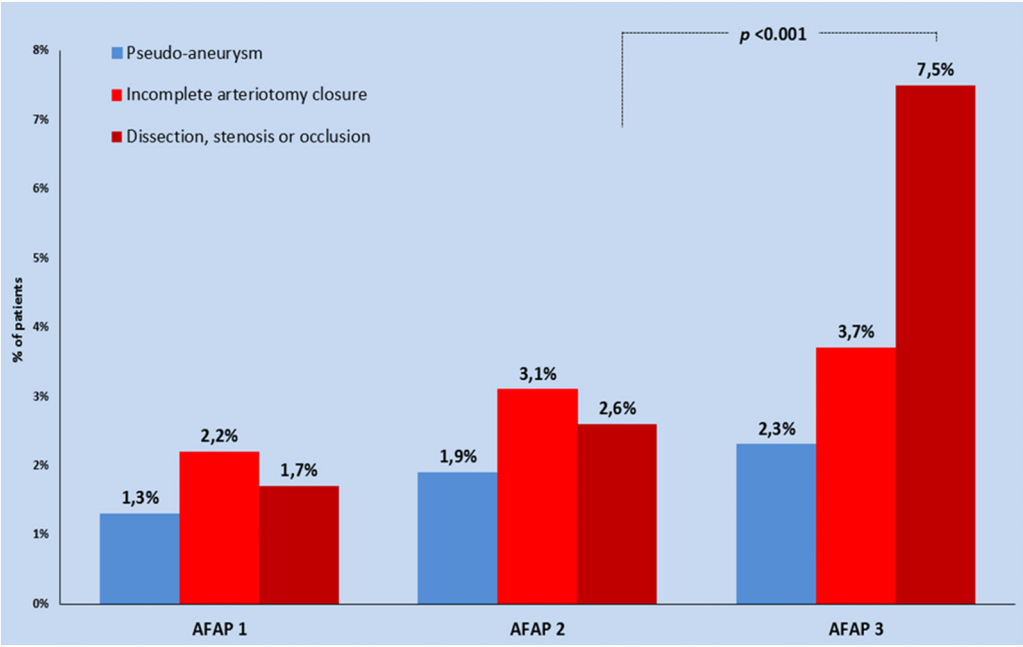

Fig. 1. Association between arteriotomy-depth/femoral-artery phenotype and the type of vascular injury. AFAP indicates arteriotomy-depth/femoral-artery phenotype.

For this reason, the MASH trial performed a head-to-head comparison of 104 patients undergoing ProGlide and 102 patients undergoing MANTA closure of large-bore arteriotomies [10]. The study found no difference in the rate of any access complications albeit that VCD failure was more common in the ProGlide group whereas bailout surgery or stenting was numerically more frequent in the MANTA group. These findings confirm that there are technology-specific mechanisms of access complications of which the clinical impact is not yet elucidated.

The present study adds to this by demonstrating that the clinical impact of access complications was acceptable given the low frequency of MANTA-related major/life-threatening bleeding. The low number of early deaths in this study (13 out of 891) of which only 1 was attributable to MANTA closure complication was also reassuring.

Nevertheless, access complications were associated with a significantly longer hospital stay. Female sex was an important predictor for access complications related to MANTA, which has repeatedly been demonstrated in prior large cardiovascular registries and trials [11,12], including the PARTNER trial that found female gender to be the only independent predictor of vascular complications [1]. Mechanisms for elevated vascular complication risk in women are complex but include variations in platelet reactivity, inappropriate dosing of anticoagulant and antiplatelet therapy and smaller caliber peripheral vessels [11].

With respect to the latter, Moccetti et al. [13] recently found iliofemoral diameter < 6 mm to be a predictor of MANTA related complications. Our results confirm that femoral dimensions matter particularly when associated with an arteriotomy depth > 40 mm. Moccetti suggested that in small femoral arteries elevation of the toggle may lead to occlusion of the artery. If true, there may be an additional risk when the target artery is not only small but also needs to traverse through deeper subcutaneous tissues generally requiring a more vertical approach for arterial access, which, during closure, may hinder to retract the VCD under the recommended 45° angle. This angle is important to achieve optimal intraluminal toggle position and avoid arterial injury such as dissection, stenosis or occlusion which were particularly prevalent in patients with an unfavorable arteriotomy-dept/femoral-diameter phenotype (AFAP-3, Fig. 1). On the other hand, it is likely that patients exhibiting such unfavorable vascular anatomy are at elevated risk for vascular injury with any type of closure technology.

Nevertheless, the predictors of access complications as found in this study can be used for risk-stratification and optimization of vascular management. Probably the most important step towards successful closure is to obtain safe vascular access using, for example, real-time ultrasound guidance as it provides precise information on vascular dimensions and pathologies, and helps localizing the optimal puncture site proximal to the bifurcation and distal to the origin of the inferior epigastric artery. Also real-time ultrasound visualization of the anchor location inside the artery may facilitate safe deployment of the MANTA VCD without dependence on preprocedure measurements (obtained from MANTA depth locator) [14].

In this study, left femoral access emerged as an important predictor of access complications. In principle in the context of large bore arterial procedures the right common femoral artery seems the access of first choice for practical and ergonomic reasons. A left femoral approach typically infers peripheral arterial disease and conceivably may make a procedure more challenging from a technical perspective when most experience has accrued from the right side. Still, however, the reason why left femoral approach independently predicted access complications while the variable peripheral arterial disease was not remains uncertain. Potentially, peripheral arterial disease lost predictive value due to the fact that severe vessel calcification and tortuosity were strict exclusion criteria.

Device profile determines arteriotomy size. Lower profile devices may therefore be associated with fewer complications. In the TAVR context, Evolut R has the lowest device profile with its InLine sheath and Enveo R delivery system. Therefore it was not surprising that Evolut R in this study was associated with (numerically) the lowest frequency of major and minor access complications compared to other valve-types (Figure in supplementary [7]).

In addition to further reductions in device profile, continuous advances in vascular closure technologies likely improves the future management of large-bore arteriotomies. It remains to be seen how the MANTA VCD performs relative to other new closure technologies such as the PerQseal (*ClinicalTrials.gov* identifier NCT03423602) and InSeal VCD [15].

4.1. Limitations

This was a nonrandomized patient-level meta-analysis enrolling patients from 2 multicenter device approval studies and 1 post-market study. Selection criteria varied and were particularly stringent in the SAFE-MANTA trial. For example, patients with poor left ventricular function and severe kidney disease were excluded whereas those with suboptimal femoral puncture location (i.e. outside the common femoral artery) were excluded during the procedure. Of note, study results are not applicable to patients with morbid obesity or extensive femoral calcification which were exclusion criteria in all 3 studies. This is also the reason that femoral calcification could not be tested for its predictive value of access complications. Also, there was no angiographic core lab to further determine vessel characteristics. Another limitation was that the relationship between sheath-size and access complications was not studied given that a substantial number of procedures were executed using expandable sheaths exhibiting a smaller outer diameter than the device/delivery catheter it accomodates. Prior studies found a clear relationship between sheath-to-femoral-artery ratio and access complications [16]. Finally, the use of ultrasound-guided arterial access was not recorded during the study and, therefore, it remains unknown to what extent the access technique influenced the risk of complications.

5. Conclusion

Large bore arteriotomy closure with MANTA VCD provided fast and safe hemostasis with an acceptable complication rate. Refined procedure planning and risk-stratification may further improve MANTA VCD performance in clinical practice.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2021.02.017.

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CRediT authorship contribution statement

Rutger-Jan Nuis: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Visualization. **David Wood:** Conceptualization, Writing – review & editing. **Herbert Kroon:** Writing – review & editing. **Maarten van Wiechen:** Writing – review & editing. **Darra Bigelow:** Writing – review & editing. **Chris Buller:** Writing – review & editing. **Joost Daemen:** Writing – review & editing. **Peter de Jaegere:** Writing – review & editing. **Zvonimir Krajcer:** Writing – review & editing. **John Webb:** Writing – review & editing. **Nicolas Van Mieghem:** Conceptualization, Methodology, Writing – review & editing.

Declaration of competing interest

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References

[1] Genereux P, Webb JG, Svensson LG, Kodali SK, Satler LF, Fearon WF, 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.
[2] Barbash IM, Barbanti M, Webb J, Molina-Martin De Nicolas J, Abramowitz Y, Latib A, et al. Comparison of vascular closure devices for access site closure after transfemoral aortic valve implantation. Eur Heart J.2015;36:3370-9.
[3] Barbanti M, Capranzano P, Ohno Y, Gulino S, Sgroi C, Imme S, et al. Comparison of suture-based vascular closure devices in transfemoral transcatheter aortic valve implantation. EuroIntervention.2015;11:690-7.
[4] Van Mieghem NM, Latib A, van der Heyden J, van Gils L, Daemen J, Sorzano T, et al. Percutaneous plug-based arteriotomy closure device for large-bore access: a multicenter prospective study. JACC Cardiovasc Interv. 2017;10:613–9.
[5] Wood DA, Krajcer Z, Sathananthan J, Strickman N, Metzger C, Fearon W, et al. Investigators SMS. Pivotal clinical study to evaluate the safety and effectiveness of the MANTA Percutaneous vascular closure device. Circ Cardiovasc Interv.2019;12:e007258.
[6] Kroon HG, Tonino PAL, Savontaus M, Amoroso G, Laine M, Christiansen EH, et al. Dedicated plug based closure for large bore access -The MARVEL prospective registry. Catheter Cardiovasc Interv.2020;97:1270-8.
[7] Nuis RJ, Wood D, Kroon H, Van Wiechen M, Bigelow D, Buller C, et al. Supplemental data plug-based large-bore arteriotomy vascular closure device related access complications data in brief 2021 [In Press].
[8] Moriyama N, Lindstrom L, Laine M. Propensity-matched comparison of vascular closure devices after transcatheter aortic valve replacement using MANTA versus ProGlide. EuroIntervention.2019;14:e1558.
[9] Biancari F, Romppanen H, Savontaus M, Siljander A, Makikallio T, Piira OP, et al. MANTA versus ProGlide vascular closure devices in transfemoral transcatheter aortic valve implantation. Int J Cardiol. 2018;263:29–31.
[10] van Wiechen MP, Tchetche D, Ooms JF, Hokken TW, Kroon H, Ziviello F, et al. Suture- or plug-based large-bore arteriotomy closure: a pilot randomized controlled trial. JACC Cardiovasc Interv. 2021;14:149–57.
[11] Chacko Y, Parikh RV, Tremmel JA. Vascular access-related complications in women: temporal trends, emerging data, and the current state of interventional cardiology practice. Curr Atheroscler Rep. 2018;20:41.
[12] Saad M, Nairooz R, Pothineni NVK, Almomani A, Kovelamudi S, Sardar P, et al. Long-term outcomes with transcatheter aortic valve replacement in women compared with men: evidence from a meta-analysis. JACC Cardiovasc Interv. 2018;11:24–35.
[13] Moccetti F, Brinkert M, Seelos R, Ockert S, Bossard M, Cuculi F, et al. Insights from a multidisciplinary introduction of the MANTA vascular closure device. JACC Cardiovasc Interv. 2019;12:1730–6.
[14] Moriyama N, Dahlbacka S, Vahasilta T, Vainikka T, Aho P, Viikila J, et al. The efficacy of the ultrasound-navigated MANTA deployment following Transfemoral Transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2019;12:2564–6.
[15] Barbash IM, Kornowski R, Berkovitch A, Assali A, Erlebach M, Guetta V, et al. Percutaneous nitinol-based vascular closure device for large bore arterial access hemostasis: results of a prospective multicenter study. Catheter Cardiovasc Interv. 2020;96:473–8.
[16] Ruge H, Burri M, Erlebach M, Lange R. Access site related vascular complications with third generation transcatheter heart valve systems. Catheter Cardiovasc Interv. 2021;97:325-32.