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ORIGINAL STUDIES

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Dedicated plug based closure for large bore access –The MARVEL prospective registry

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Abstract

Objectives: To study safety and performance of the MANTA Vascular closure device (VCD) under real world conditions in 10 centers.

Background: The MANTA is a novel plug-based device for large bore arteriotomy closure.

Methods: We included all eligible patients who underwent transfemoral large bore percutaneous procedures. Exclusion criteria were per operator's discretion and included severe calcification or marked tortuosity of the access vessel, presence of marked obesity/cachexia or a systolic blood pressure above 180 mmHg. The primary performance endpoint was time to hemostasis. Primary and secondary safety endpoints were major and minor access site related vascular complications up to 30 days, respectively. Vascular complications were adjudicated by an independent clinical event committee according to VARC-2 criteria. We performed multivariable logistic regression to estimate the effect of baseline and procedural characteristics on any and major vascular complications.

Results: Between February 2018 and July 2019 500 patients were enrolled undergoing Transcatheter aortic valve replacement (TAVR, N = 496), Balloon aortic valvuloplasty (BAV, N = 2), Mechanical circulatory support (MCS, N = 1) or Endovascular aneurysm repair (EVAR, N = 1). Mean age was 80.8 ± 6.6 years with a median STS-score of 2.7 [IQR 2.0–4.3] %. MANTA access site complications were major in 20 (4%) and minor in 28 patients (5.6%). Median time to hemostasis was 50 [IQR 20–120] sec. Severe femoral artery calcification, scar presence in groin, longer procedure duration, female gender and history of hypertension were independent predictors for vascular complications.

Conclusion: In this study, MANTA appeared to be a safe and effective device for large bore access closure under real-world conditions.

KEYWORDS

transcatheter valve implantation, vascular closure, vascular complications

1 | INTRODUCTION

Catheter based techniques have emerged to treat aorta and left-sided heart valve disease which may include mechanical circulatory support (MCS). These procedures typically require large bore arterial access. A completely percutaneous approach implies the use of closure devices to secure the arteriotomy after catheter removal, in which most experience has been accrued with suture-based closure techniques. Transcatheter aortic valve replacement (TAVR) is arguably the most common large bore arterial intervention. Recent TAVR trials in lower risk patients reported major vascular complication rates ranging between 2.2% and 7.9%.[1,2] The majority of TAVR related access site complications seem related to closure device failure.[3] A comparison of various early generation suture-based techniques resulted in conflicting results but suggested a 20% vascular complication rate.[4,5] The MANTA vascular closure device (VCD, Teleflex Inc., PA) is a novel collagen plug-based device dedicated for large bore arteriotomy closure. The CE Mark study demonstrated favorable outcomes in a small sample of 50 patients undergoing large bore interventions with MANTA closure.[6] The US based SAFE MANTA IDE trial reported high technical success with MANTA closure and a 4.2% major vascular complication rate in a selected cohort of 263 patients undergoing large bore arterial interventions.[7] The international, multi-center, prospective observational MARVEL (MAnta Registry for Vascular Large-borE CLosure) study aimed to evaluate safety and performance of MANTA closure for large bore arteriotomies in contemporary clinical practice.

2 | METHODS

2.1 | Patient selection and study protocol

Patients undergoing completely percutaneous transfemoral large bore arterial interventions were eligible for the study. A total of 500 patients were enrolled by 10 hospitals in Canada, Denmark, Netherlands, Finland and Switzerland. All patients were discussed in a multidisciplinary (heart) team meeting including (interventional) cardiologists and cardiothoracic or vascular surgeons. Preprocedural planning with multi-detector computed tomography was mandatory for all TAVR procedures and recommended for other interventions such as MCS, balloon aortic valvuloplasty (BAV) or endovascular aneurysm repair (EVAR). Femoral artery calcification at access site level was classified according to the semi-quantitative MANTA Femoral Artery Calcification Score (MFACS, Supplementary Figure 1) as follows:

Stage 0: No calcification.

Stage 1: Small calcium spots dispersed over the vessel surface.

Stage 2: Calcium plaques dispersed over the vessel surface.

Stage 3: Large calcium plaque at the posterior wall.

Stage 4: Large calcium plaque at the anterior wall.

Stage 5: Excessive and circumferential calcium.

Relative exclusion criteria for MANTA use were per operator's discretion and included (1) excessive calcification of the access vessel; (2) severe peripheral artery disease preluding safe introduction of a large arterial sheath; (3) marked tortuosity of the femoral or iliac artery; (4) body mass index > 40 kg/m^2 (5) body mass index < 20 kg/m^2 and (6) uncontrolled hypertension at baseline (systolic blood pressure > 180 mmHg). All participating operators had performed at least 10 MANTA closures prior to study entry. All interventions were performed with unfractionated heparin and target activated clotting time at the time of MANTA closure needed to be < 250 s. Protamine use was per operator's decision. A femoral angiogram post-MANTA deployment was recommended for all patients. Clinical examination of the MANTA access site for complications was mandatory directly and 24 hours after the index procedure and also before hospital discharge. Clinical follow up was planned at 30 days. Every patient signed informed consent for the index procedure and trial enrollment. MARVEL was conducted in compliance with the declaration of Helsinki, Good Clinical Practice principles and current International Standard

for Clinical Investigations of medical devices for human subjects (EN-ISO 14155:2011). The Institutional Review Board of each institution approved the design of present study. MARVEL was registered under the Identifier NCT03330002.

2.2 | The MANTA device

The MANTA VCD consists of a delivery system and an implantable closing unit which comprises a bioresorbable (poly-lactic-co-glycolic acid) toggle inside the vessel and a hemostatic bovine collagen plug outside the vessel (Figure 1). The latter two are connected with a non-resorbable polyester suture and a stainless-steel lock. Prior to large sheath insertion, arteriotomy depth is determined with an 8F depth locator with centimeter markers (Supplementary Figure 2). At the end of the procedure the large sheath is exchanged for the dedicated 14F or 18F MANTA sheath with centimeter markers that accommodate the delivery unit. The combined assembly is then withdrawn over the wire to the designated arteriotomy depth. The toggle is released by turning the lever on the handle. Subsequently, the assembly is then further withdrawn until a green color code is seen on the handle, that denotes sufficient pulling force. The collagen plug is delivered towards the vessel by sliding down the tamper tube. The wire is removed, and the MANTA suture is cut at skin level. All MANTA components are resorbed within 6 months apart from the stainless-steel lock. Arterial sheaths sizes 10 – 14F (maximum outer diameter of 18F) and 14 – 20F (maximum outer diameter of 25F) require a 14F and 18F MANTA device, respectively.

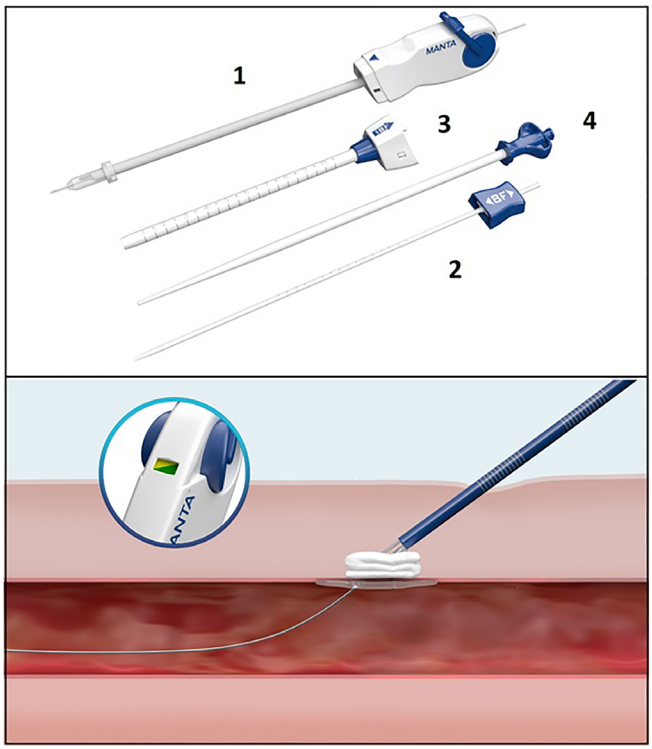

FIGURE 1 The 18F MANTA device. 1. Delivery system and closing unit. 2. Puncture location dilator 3. Dedicated MANTA sheath 4. Sheath introducer. The 18F system has a blue color, the 14F system has an orange color. The lower part illustrates the toggle on the inside of the vessel and the collagen plug on the outside. Also notice the green color on the delivery unit when sufficient pulling force is applied when withdrawing the MANTA assembly (dedicated sheath and delivery unit) from the artery [Color figure can be viewed at wileyonlinelibrary.com]

2.3 | Clinical endpoints

The primary and secondary safety endpoints were the occurrence of major and minor MANTA access site related vascular complications up to 30 days, respectively. All clinically relevant endpoints related to the MANTA access site were adjudicated according to the Valve Academic Research Consortium (VARC) 2 criteria by an independent Clinical Event Committee.[8] The adjudication committee consisted of physicians outside the participating centers who received a fee by the investigators from the unrestricted grant to execute the trial. The primary performance endpoint was time to hemostasis, which was defined as the elapsed time between MANTA deployment (withdrawal of dedicated MANTA sheath from artery) and observed arterial hemostasis (no or minimal subcutaneous oozing and the absence of expanding or developing hematoma).

2.4 | Data collection and monitoring

Baseline and procedural characteristics, follow-up data as well as adverse events were entered into an electronic data capture system. Accuracy of data and compliance with regulatory agreements related to study conduction was monitored by an independent clinical research organization, Factory-CRO (Bilthoven, The Netherlands). Additionally, an independent auditor (Phase More, Nijmegen, The Netherlands) visited the highest enrolling center to ensure compliance with Good Clinical Practice principles and ISO 14155:2011 and to perform source verification as well.

2.5 | Statistical analysis

Continuous variables were presented as mean (±SD) or median (interquartile range) and categorical variables as n (%). The distribution of continuous variables was examined for normality through histograms and Q-Q plots. For the comparison of categorical variables between the different transcatheter heart valves we used the Pearson $\chi 2$ or Fisher exact test as appropriate. For ensuing pairwise comparisons, we applied Bonferroni corrections to account for multiple testing. Additionally, we performed multivariable logistic regression to estimate the effect of relevant baseline and procedural characteristics on occurrence of any (major) vascular complications after MANTA closure. We entered those variables that displayed a p-value of less than 0.10 in univariate analysis. When limited number of events were present, we chose those variables that had a p-value less than 0.10 and are known risk factors for

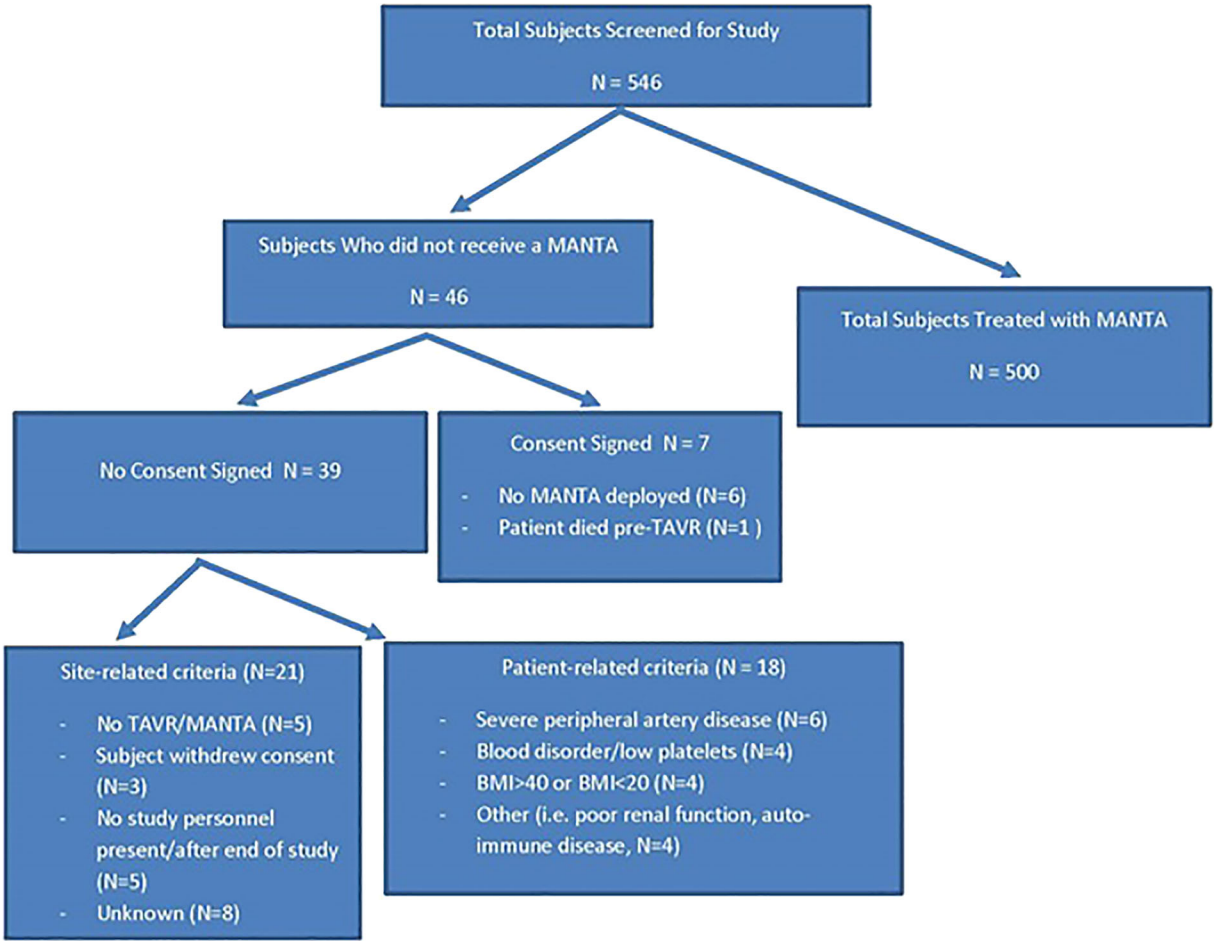

FIGURE 2 Flowchart describing study inclusion [Color figure can be viewed at wileyonlinelibrary.com]

the occurrence of peripheral artery disease or vascular complications or could theoretically increase the risk of vascular complications (severe femoral artery calcification defined as MFACS ≥ 3, groin scarring from previous procedures, arteriotomy depth). All statistical analyses were performed with SPSS version 25.0 (IBM Corp., N Y).

3 | RESULTS

Between February 2018 and July 2019, a total of 500 patients were included. A flowchart describing patient inclusion is displayed in Figure 2. Table 1 summarizes baseline demographics. Almost half of patients were female (N = 226, 45%), mean age was 80.8 ± 6.6 years and the Society of Thoracic Surgery (STS) predicted risk of mortality was 2.7 [IQR 2.0–4.3] %. Most patients (N = 496, 99%) underwent a TAVR procedure with either the Sapien 3 (Ultra) (N = 203–41%, Edwards Lifesciences, CA), Evolut R/PRO (N = 202–40%, Medtronic Inc., MN) or ACURATE neo valve (N = 72–14%, Boston Scientific, MA), while two patients underwent BAV. One patient underwent an EVAR procedure and another patient underwent a high risk percutaneous coronary intervention (PCI) requiring MCS. Procedural data are tabulated in Table 2 and used sheaths in Supplementary Table 1.

3.1 | Primary endpoint

The primary performance endpoint of time to hemostasis was a median of 50 [IQR 20–120] sec as displayed in Table 3 and Supplementary Figure 3. Overall, time to hemostasis ranged from 0 s up to 75 min. More than half of patients (N = 269, 54%) reached hemostasis within 1 min and cumulatively 421 (84%) patients had hemostasis within 5 min. When manual compression was required, the median time to hemostasis was 7 [IQR 2 to 12] min (range 55 s - 16 min). The primary endpoint of major vascular complications related to the MANTA access site occurred in 20 patients (4.0%): immediate MANTA closure device failure in 7 (sometimes combined), large hematoma requiring red blood cell (RBC) transfusion in 4 and flow limiting dissection or stenosis in 4. The remaining patients suffered from rupture or perforation (N = 3), distal embolization (N = 2), pseudoaneurysm (N = 2) or ipsilateral lower extremity ischemia (N = 1). These patients were treated with surgery (N = 12), ballooning (N = 2) or deployment of a covered stent (N = 3). One patient required ambulatory surgery due to a pseudoaneurysm 2 weeks after a major vascular complication and subsequent bleeding. Five patients were in need of surgery due to uncontrolled bleeding. One of these suffered a retroperitoneal bleeding and needed 8 RBC transfusions. Four patients

TABLE 1 Baseline characteristics of the enrolled patients

	Number of patients (N = 500)
Baseline characteristics	
Female gender	226 (45%)
Age (years)	80.8 ± 6.6
STS score (%)	2.7 [IQR 2.0–4.3][a]
Body mass index (kg/m^2)	26.9 ± 4.3
History of PCI	144 (29%)
History of CABG	53 (11%)
Hypertension	323 (65%)
History of stroke	85 (17%)
Peripheral artery disease	40 (8%)
Pacemaker at baseline	43 (9%)
Glomerular filtration rate < 60 mL/min	226 (45%)
Left ventricular ejection fraction <20%	2 (< 1%)
Antithrombotic therapy at baseline	
Acetylsalicylic acid	286 (57%)
Clopidogrel or other P2Y12 inhibitor	200 (40%)
Oral anticoagulation	66 (13%)
New oral anticoagulation	61 (12%)
Heparin or low molecular weight heparin	14 (3%)

Note: Categorical variables are shown as N (%). Continuous variables are displayed as mean ± SD or median [IQR].
Abbreviations: CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; STS, society of thoracic surgeons.
[a]Aarhus University Hospital and Vancouver General Health did not provide STS-scores.

needed vascular repair surgery for a large hematoma or flow limiting dissection/stenosis. Two patients required surgery due to MANTA embolization distally. The MANTA needed to be explanted in five and thrombendarteriectomy was performed in four subjects. Three patients required no treatment or just prolonged manual compression. A total of 12 patients required RBC transfusions. All major vascular complications occurred on the procedure day. No significant differences in major vascular complication rates were observed between valve types (Supplementary Figure 4).

3.2 | Secondary endpoint and overall 30 day clinical outcomes

Twenty-eight patients (5.6%) suffered a minor vascular complication after MANTA deployment and included (sometimes combined) nine dissections, seven pseudoaneurysms, six hematomas, five immediate MANTA closure device failures and three stenoses. These patients were treated with minor surgery (N = 2), ballooning (N = 5) or a covered stent (N = 4). One patient underwent surgery due to uncontrolled bleeding and one required vascular repair due to a flow limiting stenosis. Five patients required lidocaine/epinephrine combination or thrombin injection, but the majority did not require treatment (N = 6) or just prolonged manual compression (N = 6). Three patients required a RBC transfusion. All minor vascular complication occurred on the procedure day, except for three patients 1 day later. Seven patients (1%) died during the follow-up period of 40 ± 13 days. One patient died due to shock because of external iliac artery rupture after BAV. That patient had severe femoral artery calcification and a too high femoral puncture was performed. There was no hemostasis after MANTA closure. Hemostasis was achieved with an occlusion balloon in the abdominal aorta. After leaving the catheterization laboratory, the patient developed gradual hypotension and underwent urgent vascular surgery. However, the patient developed multi-organ failure and died the same day in the ICU. Twenty-five (5.0%) patients suffered a bleeding event, 10 major and 6 life-threatening. In total, 16 patients needed red blood cell transfusions. In one patient the bleeding was not access related. Four out of six patients with a disabling bleeding needed red blood cell transfusions (2–8 transfusions). Seventy percent (N = 7 out of 10) of the patients with a major bleeding required blood transfusions and eventually stenting or surgery. Thirteen percent of patients needed a new permanent pacemaker implantation (61/457, Supplementary Table 2). Acute kidney injury (stage I or II) occurred in three patients and major stroke struck 2% of patients (N = 9). Overall 22 patients (4.4%) suffered a vascular complication not related to the MANTA access site (i.e., pericardial tamponade or related to contralateral access closure), of which six were major. Some patients who suffered a vascular complication on the MANTA side also developed non-MANTA related vascular complications elsewhere.

3.3 | Predictors of vascular complications with MANTA closure

In univariate analysis age, STS-score, history of hypertension, chronic kidney disease, groin scar from previous surgery, a MFACS score ≥ 3, female gender and longer procedure duration were associated with the occurrence of any vascular complication after MANTA closure (Supplementary Table 3). In multivariable analysis, groin scarring from a previous procedure (OR 16.55, 95% CI 2.72–100.59, p = .002), MFACS score ≥ 3 (OR 2.72, 95% CI 1.06–7.03, p = .038), duration of procedure (OR 1.04, 95% CI 1.02–1.05, p = .0005), hypertension (OR 2.82, 95% CI 1.14–6.97, p = .025) and female gender (OR 2.13, 95% CI 1.05–4.34, p = .037) remained independent predictors for any vascular complication (Table 4). For major vascular complications the predicting variables were similar, however gender and history of hypertension seemed less important (Supplementary Tables 4 and 5).

4 | DISCUSSION

The main findings of this prospective, multicenter, post-market study can be summarized as follows: (a) The MANTA VCD appeared to be

TABLE 2 Procedural characteristics

	Left side N = 61	Right side N = 440	Combined N = 500[a]
Procedural characteristics			
Access through femoral artery	61 (12%)	440 (88%)	500 (100%)
Common femoral artery diameter (mm)	7.49 ± 2.15	7.94 ± 1.45	7.88 ± 1.55
Sheath-to-femoral-artery ratio	1.05 ± 0.30	0.97 ± 0.20	0.98 ± 0.21
Calcification of the femoral artery (MFACS)			
0–1 no or minimal	28 (46%)	317 (73%)	345 (69%)
2 moderate	20 (33%)	82 (19%)	102 (20%)
3–5 severe or circumferential	13 (21%)	35 (8%)	48 (10%)
Unknown	0 (0%)	6 (1%)	6 (1%)
Scar in groin from previous surgery	2 (3%)	6 (1%)	8 (2%)
Procedure duration (min)	72 ± 31	64 ± 28	65 ± 28
Activated clotting time before closure (sec)	203 ± 50	181 ± 61	184 ± 60
Systolic blood pressure before closure (mmHg)	143 ± 22	133 ± 24	134 ± 24
Protamine used before closure	30 (49%)	266 (61%)	296 (59%)
Protamine used after closure	9 (15%)	50 (11%)	59 (12%)
Type of procedure			
TAVR	59 (96%)	437 (99%)	496 (99%)
Edwards Sapien3/Sapien3 ultra	17 (28%)	186 (41%)	203 (41%)
Medtronic Evolut R	18 (30%)	64 (15%)	82 (16%)
Medtronic Evolut PRO	15 (25%)	105 (24%)	120 (24%)
Symetis Acurate neo	7 (12%)	65 (15%)	72 (14%)
St. Jude portico	1 (2%)	11 (3%)	12 (2%)
New valve technology Allegra	1 (2%)	5 (1%)	6 (1%)
Boston Scientific lotus	-	1 (< 1%)	1 (< 1%)
High risk PCI with Impella MCS	-	1 (< 1%)	1 (< 1%)
BAV	1 (2%)	1 (< 1%)	2 (< 1%)
EVAR Gore excluder C3	1 (2%)	1 (< 1%)	1 (< 1%)
MANTA characteristics			
14 French (F)	5 (8%)	13 (3%)	18 (4%)
18 French (F)	56 (92%)	423 (96%)	479 (96%)[b]
Tissue/Arteriotomy depth (cm)	3.7 ± 1.3	3.6 ± 1.1	3.6 ± 1.2

Note: Categorical variables are shown as N (%). Continuous variables are displayed as mean ± SD.

Abbreviations: BAV, balloon aortic valvuloplasty; EVAR, endovascular aneurysm repair; F, French; MCS, mechanical circulatory support; PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement.

[a]One patient underwent EVAR requiring access through both sides.

[b]For 4 MANTA implantations the F size was unavailable.

safe for usage in completely percutaneous large bore access procedures. (b) Time to hemostasis is short with a median time of 50 [IQR 20–120] sec. (c) MANTA use was associated with a 4% major and 5.6% minor vascular complication rate. (d) Corrective vascular surgery was required in 2.8% of cases. (e) Scarring around the puncture site from previous surgery, procedure duration, excessive femoral calcifications, hypertension and female gender were associated with MANTA access site vascular complications.

The MARVEL trial mirrors the SAFE MANTA IDE trial that reported a 4.2% major MANTA vascular complication rate in 263 selected patients aged 79.4 ± 8.4 years old with a mean STS-score of 4.45 ± 3.04%. Notably, the SAFE MANTA trial applied more stringent inclusion/exclusion criteria and MARVEL doubled the sample size. MARVEL therefore appears to confirm MANTA safety in a broader population and its feasibility in real world clinical practice. Multiple retrospective studies on MANTA reported minor and major vascular complication rates between 0.0%–6.0% and 1.1%–9.3%, respectively.[6,9-12] Notably, the majority of patients in MARVEL underwent TAVR. Major vascular complications rates in recent TAVR trials including patients at low or intermediate operative risk vary between 2.0% and 7.9%.[1,2] With a mean age of 80.8 ± 6.6 years old, an STS-score of 2.7 [IQR 2.0–4.3] % and peripheral artery disease prevalence

TABLE 3 Overview of 30-day clinical outcomes

	Number of patients (N = 500)
30-day outcomes	
Mean follow-up (days)	40 ± 13
Manta related major vascular complication	20 (4.0%)
Manta related minor vascular complication	28 (5.6%)
Bleeding	
Minor bleeding	9 (1.8%)
Major bleeding	10 (2.0%)
Disabling bleeding	6 (1.2%)
Red blood cell transfusions	
1 packed cell	4 (0.8%)
2 packed cells	8 (1.6%)
3 packed cells	2 (0.4%)
4 packed cells	1 (0.2%)
8 packed cells	1 (0.2%)
Percutaneous closure device failure	12 (2.4%)
Median time to hemostasis (s)	50 [20–120]

Note: Categorical variables are shown as N (%). Continuous variables are displayed as mean ± SD or median [IQR].

TABLE 4 Multivariable analysis on the occurrence of any vascular complication

	Any vascular complication OR (95% CI)	*P* value
Baseline characteristics		
Scar in groin from previous procedure	16.55 (2.72–100.59)	.002
Glomerular filtration rate < 60 mL/min	1.74 (0.87–3.51)	.12
Severe calcification (MFACS score 3 or greater)	2.72 (1.06–7.03)	.038
Duration of procedure (per minute increase)	1.04 (1.02–1.05)	.0005
Female gender	2.13 (1.05–4.34)	.037
Hypertension	2.82 (1.14–6.97)	.025

Note: Variables are shown as odds ratio OR (95% confidence interval).
Abbreviations: MFACS, MANTA femoral artery calcification score.

of 8.0%, MARVEL arguably included patients at intermediate risk and complication rates might be lower in younger and truly low risk patients. In MARVEL all access complications clustered within the first 24 hours after closure. This is relevant in view of contemporary trends to implement early discharge (i.e., < 48 hours) protocols with TAVR. The Multidisciplinary, Multimodality, But Minimalist Transcatheter Aortic Valve Replacement (3 M TAVR) trial prospectively confirmed safety and efficacy of early discharge after the index procedure with a minimalistic or simplified TAVR approach.[13] Inherent to early discharge is safe, reliable and durable arteriotomy closure. Because we did not observe any late MANTA failures, plug-based closure may complement early discharge. Conversely, patients suffering vascular complications would demand close clinical follow-up.

Most clinical experience in terms of large bore arteriotomy closure accumulated with suture-based Proglide and Prostar (both Abbott Vascular, CA) devices. The CONTROL multi-center study was a propensity matched comparison of Proglide vs. Prostar XL in 944 patients and reported an overall 20% vascular complication rate with more major vascular complications with Prostar XL (7.4% vs. 1.9%, $p < .001$).[5] Single-center data from Catania presented conflicting data with more vascular complications with Proglide vs. Prostar (24% vs. 11.4%, $p = .007$).[4] Both studies were performed with early generation suture based closure devices and enrolled patients had more often peripheral artery disease. Thus, these results may not be a true reflection of current practice. Recently, an observational study comparing MANTA (N = 168) with Prostar XL (N = 198) found much lower major vascular and bleeding complication rates with the suture based device than reported earlier and comparable between both closure techniques (0.6% vs. 1.0%, $p = .661$ and 0.6% vs. 1.5%, $p = .102$, respectively).[14] Minor vascular and bleeding complications seemed somewhat more frequently observed with Prostar XL (10.7% vs 18.8%, $p = .003$ and 13.7% vs. 19.7%, $p = .08$, respectively).[14] In a retrospective TAVR study, Hoffmann et al compared 75 Manta with 76 Proglide closures and reported fewer vascular complications and need for bail out surgery/interventions with suture-based closure.[9] Three other comparative retrospective studies reported no difference in vascular complications between MANTA and Proglide closure strategies albeit MANTA was consistently associated with less bleeding events, fewer RBC transfusions and shorter in-hospital stay.[10-12] However, the non-randomized fashion of these studies precludes any definite conclusions. Importantly, our corrective surgery rate of 2.8% is comparable with the 2.0% and 0.8% found in the highly selected patients in the CE MARK and SAFE MANTA trials.[6,7] Surgery rates varied between 1.3% to 5.6% for the ProStar and 1.1% to 4.0% for ProGlide closures in the literature.[4,5] Of note, the retrospective studies comparing MANTA with ProGlide show comparable rates of bail-out corrective surgery.[10,12] Besides corrective surgery, the risk for infection due to the collagen pad may be relevant. This pad may function as a culture medium with a direct pathway to the skin. Also, stenosis or occlusion may occur at the site of MANTA deployment. In our study, we did not observe plug infections. Femoral artery stenosis/occlusion occurred in 7 patients (1.4%), which can be treated with ballooning from the contralateral side or eventually surgery. The SAFE MANTA trial followed up patients at 30 and 60 days with femoral ultrasound and ankle brachial index.[7] The ankle brachial index remained comparable throughout the study period and no major complications occurred after discharge date. However, CoreLab ultrasound analysis found 18 access site related events, all requiring no treatment. This included 4 cases of oozing (1.5%), 5 cases of hematoma/ecchymosis (1.9%), femoral artery stenosis (N = 1, 0.4%), intimal defect (N = 1, 0.4%) and arterial thrombosis (N = 1, 0.4%). No

infection of the collagen plug was reported. In our study, four patients underwent thrombendarteriectomy during vascular surgery. No cases of late thrombosis were reported. Arguably, suture-based closure may come with a longer learning curve including the need for multiple devices and experience with a preclosure technique. Conversely and as opposed to MANTA closure, suture-based closure may herald more catheter-based bail out options in case of failed arteriotomy closure with the application of multiple suture- or plug based closure devices. To be able to react quickly in case of failed MANTA closure, contralateral access may provide ways to stop the bleeding (i.e., contralateral ballooning). Multivariable logistic regression analysis found several risk factors for developing vascular complications after MANTA closure. Scarring in the groin due to previous procedures with femoral access may result in adhesions and more difficulty to access the femoral artery. Therefore, presence of subcutaneous scar tissue may impede complete apposition of the collagen plug. This mechanism has been shown to lead to bleeding complications and pseudoaneurysm formation in a paper analyzing MANTA-associated vascular complications.[15] Also, severe femoral artery calcification is an established risk factor for TAVR related vascular complications.[16] We strongly recommend a femoral angiogram after large bore arteriotomy closure, particularly in patients with moderate to severe femoral calcification and/or history of percutaneous femoral procedures. Also, in case of severe (anterior) femoral artery calcification, ultrasound guidance may help to select the most preferable segments to access. Importantly, as suggested by others, we would advise against too high femoral punctures close to the inguinal ligament.[15] Presence of the (more dense) inguinal ligament may impede or result in more difficulty achieving complete collagen plug apposition. Furthermore, advanced chronic kidney disease is associated with accelerated atherosclerosis and thus related to worse outcomes after TAVR on the short- and long-term.[17] Longer procedure time may imply added complexity, including challenging access, and therefore might indicate a higher risk for vascular complications. Lastly, female gender consistently was associated with more TAVR related vascular complications. Women have on average smaller artery sizes and, with the relatively large sheath diameters needed for TAVR, this may increase the risk for vascular complications. Further research is required to optimize procedural planning, risk stratification for vascular complications and potentially patient specific closure device selection. In that regard, the MASH (MAnta versus Suture-based closure after transcatHeter aortic valve implantation) trial (NCT03811119) is a prospective 2-center randomized comparison between plug and suture based arteriotomy closure that recently completed its enrollment of 210 TAVR patients.

4.1 | Study limitations

MARVEL was a multicenter, prospective study without randomization and could be prone to selection bias. Also, femoral angiography after large bore closure was recommended but not mandated and also site reported. Femoral angiography assessment by an independent core laboratory could have enhanced the overall phenotyping of the access site and further scrutinized closure success. Still, it is the largest prospective study on this topic to date. Its multi-center design and only relative exclusion criteria make it a realistic reflection of contemporary clinical practice. Access technique (i.e., ultrasound guidance) may affect clinical outcome but was not captured in this trial to reflect each center's every day clinical practice. MARVEL was a post-market study and aimed to enroll a relatively unselected every-day practice population. However, patient enrollment needs to be seen in perspective of local practices and dynamics and thus selection bias cannot be excluded.

5 | CONCLUSION

In this present study, MANTA VCD appeared to be a safe and effective device for large bore access closure under real-world conditions.

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CONFLICTS OF INTEREST

Herbert G. Kroon MD: No conflicts of interest to declare.
Pim A.L. Tonino MD PhD: No conflicts of interest to declare.
Mikko Savontaus MD PhD: Is a proctor/consultant for Boston Scientific and Medtronic.
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DATA AVAILABILITY STATEMENT

Data is available upon reasonable request from the corresponding author.

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REFERENCES

1. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2016;374:1609-1620.
2. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019;380:1695-1705.
3. Van Mieghem NM, Tchetche D, Chieffo A, et al. Incidence, predictors, and implications of access site complications with transfemoral transcatheter aortic valve implantation. Am J Cardiol. 2012;110:1361-1367.
4. Barbanti M, Capranzano P, Ohno Y, et al. Comparison of suture-based vascular closure devices in transfemoral transcatheter aortic valve implantation. EuroIntervention. 2015;11:690-697.
5. Barbash IM, Barbanti M, Webb J, et al. Comparison of vascular closure devices for access site closure after transfemoral aortic valve implantation. Eur Heart J. 2015;36:3370-3379.
6. Van Mieghem NM, Latib A, van der Heyden J, et al. Percutaneous plug-based Arteriotomy closure device for large-bore access. A Multicenter Prospective Study JACC Cardiovasc Interv. 2017;10:613-619.
7. Wood DA, Krajcer Z, Sathananthan J, et al. Pivotal clinical study to evaluate the safety and effectiveness of the MANTA percutaneous vascular closure device. Circ Cardiovasc Interv. 2019;12:e007258.
8. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the valve academic research Consortium-2 consensus document. Eur Heart J. 2012;33:2403-2418.
9. Hoffmann P, Al-Ani A, von Lueder T, et al. Access site complications after transfemoral aortic valve implantation - a comparison of Manta and ProGlide. CVIR Endovasc. 2018;1:20.
10. Biancari F, Romppanen H, Savontaus M, et al. MANTA versus ProGlide vascular closure devices in transfemoral transcatheter aortic valve implantation. Int J Cardiol. 2018;263:29-31.
11. De Palma R, Settergren M, Ruck A, Linder R, Saleh N. Impact of percutaneous femoral arteriotomy closure using the MANTA(TM) device on vascular and bleeding complications after transcatheter aortic valve replacement. Catheter Cardiovasc Interv. 2018;92:954-961.
12. 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-e1565.
13. Wood DA, Lauck SB, Cairns JA, et al. The Vancouver 3M (multidisciplinary, multimodality, but minimalist) clinical pathway facilitates safe next-day discharge home at low-, medium-, and high-volume Transfemoral Transcatheter aortic valve replacement centers: the 3M TAVR study. JACC Cardiovasc Interv. 2019;12:459-469.
14. Gheorghe L, Brouwer J, Mathijssen H, et al. Early outcomes after percutaneous closure of access site in transfemoral transcatheter valve implantation using the novel vascular closure device collagen plug-based MANTA. Am J Cardiol. 2019;124:1265-1271.
15. Moccetti F, Brinkert M, Seelos R, et al. Insights from a multidisciplinary introduction of the MANTA vascular closure device. JACC Cardiovasc Interv. 2019;12:1730-1736.
16. Sinning JM, Horack M, Grube E, et al. The impact of peripheral arterial disease on early outcome after transcatheter aortic valve implantation: results from the German Transcatheter aortic valve interventions registry. Am Heart J. 2012;164:102-10 e1.
17. Dumonteil N, van der Boon RM, Tchetche D, et al. Impact of preoperative chronic kidney disease on short- and long-term outcomes after transcatheter aortic valve implantation: a pooled-RotterdAm-Milano-Toulouse in collaboration plus (PRAGMATIC-plus) initiative substudy. Am Heart J. 2013;165:752-760.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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