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ORIGINAL RESEARCH

Suture-based versus plug-based closure for large-bore arterial access: an individual patient-level meta-analysis of randomised trials

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ABSTRACT

BACKGROUND: Percutaneous large-bore arteriotomy closure devices are either suture- or plug-based. The comparative efficacy and safety of both techniques and optimal patient selection remain controversial.

AIMS: We aimed to conduct a patient-level meta-analysis of randomised trials comparing suture-based ProGlide versus plug-based MANTA large-bore vascular closure devices (VCDs).

METHODS: We searched PubMed, the Cochrane Central Register of Controlled Trials, and Google Scholar for randomised controlled trials comparing vascular closure with the ProGlide-based and the MANTA-based technique. The primary endpoint of this analysis was access site-related vascular complications defined according to the Valve Academic Research Consortium-3 criteria.

RESULTS: We identified 2 trials that enrolled a total of 722 patients undergoing transcatheter aortic valve implantation. The primary endpoint was significantly less common after vascular closure with the ProGlide-based technique (odds ratio [OR] 0.54, 95% confidence interval [CI]: 0.35-0.82). Access site-related bleeding events were also less common with the ProGlide-based technique (OR 0.41, 95% CI: 0.18-0.94). Prespecified subgroup analyses did not reveal any subgroup favouring the plug-based technique. Clinical outcomes with the MANTA-based technique were better in larger-sized vessels. Patients who received the ProGlide-based technique were less likely to undergo endovascular stenting or vascular surgery (OR 0.22, 95% CI: 0.06-0.79).

CONCLUSIONS: In this patient-level meta-analysis of randomised trials, the ProGlide-based technique for large-bore arterial access was superior to the MANTA-based technique in terms of vascular and bleeding complications.

KEYWORDS: large-bore vascular closure; MANTA; ProGlide; vascular closure device; vascular complications

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Vascular closure is an integral aspect of percutaneous procedures requiring large-bore arterial access, and closure device failure resulting in vascular complications is associated with increased morbidity and mortality[1-3]. The need for safe and effective percutaneous closure techniques following large-bore arterial access is expanding, particularly with the increasing volumes of transcatheter aortic valve implantation (TAVI), endovascular aortic repair, and temporary transcatheter mechanical circulatory support[4-7].

For many years, suture-based vascular closure devices (VCDs) were the only available option for large-bore arteriotomy closure. Closure techniques utilising the ProGlide VCD (Abbott) demonstrated fewer vascular and bleeding complications compared to other commercially available suture-based devices[8,9]. For closing large-bore vascular access, two ProGlide VCDs are typically applied in a crossed configuration. However, excellent outcomes have also been reported with parallel deployment[10], and the combination of one or more ProGlide VCDs with a small plug-based VCD (e.g., Angio-Seal [Terumo]) has also demonstrated considerable success and is gaining wider adoption[11,12]. Recently, a variety of dedicated non-suture-based large-bore vascular closure techniques have been developed, and among these, the plug-based MANTA VCD (Teleflex) has emerged as the most extensively studied and widely used device. The MANTA VCD utilises a sandwich technique, combining intraluminal polymer toggles with an extraluminal collagen plug to close the arterial puncture site[13].

Two randomised controlled trials (RCTs) have compared the suture-based ProGlide and the plug-based MANTA techniques in patients undergoing transfemoral TAVI. The MASH-TAVI Trial found no significant differences between the two techniques in terms of access site bleeding or vascular complications[14]. However, the trial may have been underpowered. The larger CHOICE-CLOSURE trial reported a higher incidence of access site-related vascular complications with the MANTA-based technique[15]. Several meta-analyses combining both RCTs and observational studies found no significant differences between the two closure techniques in terms of access site-related vascular complications[9,16,17]. However, a recent meta-analysis of published results from RCTs and observational studies yielded conflicting findings. Observational studies reported fewer vascular complications with the MANTA-based technique, while RCTs favoured the ProGlide-based technique[18]. This discordant outcome suggests the presence of relevant confounding factors in the published observational studies.

To date, a patient-level meta-analysis of published RCTs allowing meaningful subgroup comparisons has not been performed. Additionally, CHOICE-CLOSURE and MASH-TAVI used partially different endpoint definitions, and neither assessed endpoints according to the most recent Valve Academic Research Consortium (VARC)-3 criteria[19]. To address these limitations, we conducted an individual patient-level meta-analysis of RCTs comparing the ProGlide-based technique and the MANTA-based technique in large-bore (≥12 Fr) arterial access procedures utilising contemporary endpoint definitions.

Impact on daily practice

Percutaneous large-bore arteriotomy closure methods are either suture-based (ProGlide vascular closure device) or plug-based (MANTA vascular closure device), but the efficacy and safety of both techniques remain controversial. In this patient-level meta-analysis of randomised trials, the ProGlide-based technique for large-bore arterial access was superior to the MANTA-based technique in terms of vascular and bleeding complications. Clinical outcomes with the MANTA-based technique improved as the vessel size increased. Further studies are needed to enable individualised selection of the vascular closure technique based on specific patient characteristics.

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Methods

SEARCH STRATEGY AND SELECTION CRITERIA

The reporting of this collaborative meta-analysis follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses of Individual Patient Data (PRISMA-IPD) statement (PRISMA-IPD Checklist is provided in **Supplementary Appendix 1**)[20]. We searched PubMed, the Cochrane Central Register of Controlled Trials, and Google Scholar for trials registered or published between 1 January 2016 and 1 September 2024. The search period started in the year of the European Conformity (CE) certification of the MANTA VCD. The online search was performed in September 2024. Specific search strategies are detailed in **Supplementary Appendix 2**. Eligible for inclusion in this meta-analysis were registered or published RCTs comparing the ProGlide-based with the MANTA-based technique in patients undergoing procedures with large-bore (≥12 Fr) arterial access. Only trials whose investigators agreed to collaborate and provide individual patient data were included. All included trials had individual ethical approval.

DATA EXTRACTION

Two independent investigators (O. Dumpies and A. Jobs) conducted a literature search using the pre-established search terms. All studies that did not meet the eligibility criteria were excluded. In cases of discrepancy, the results were discussed with a third investigator (M. Abdel-Wahab). Patient-level data were requested for studies that met the eligibility criteria. A prepared datasheet was provided to the coordinating investigators for data extraction to ensure uniform coding of data, and all trial data were then combined into a single database. Discrepancies, inconsistencies, and incomplete data were checked against published reports to ensure the integrity of the combined database. In addition, missing data were

Abbreviations

TAVI transcatheter aortic valve implantation **VARC** Valve Academic Research Consortium **VCD** vascular closure device

retrospectively extracted from the original trial documentation by the respective coordinating investigator and their trial team. The risk of bias was assessed by two independent investigators (O. Dumpies and A. Jobs) according to the scheme provided by the Cochrane Handbook for Systematic Reviews of Interventions[21] **(Supplementary Table 1)**.

STUDY OUTCOMES

The primary endpoint of this analysis was in-hospital major and minor main access site-related vascular complications, defined according to VARC-3[19]. A detailed definition of access site-related vascular complications with the respective components is given in **Supplementary Table 2**. The primary endpoint was also analysed in predefined subgroups: sex (female vs male), age (75 years or younger vs older than 75 years), body mass index, anticoagulation (no vs yes), peripheral artery disease (no vs yes), access site common femoral artery diameter (less than 7 mm vs at least 7 mm), distribution of access site vascular calcification (non-anterior vs anterior), severity of access site vascular calcification (none vs mild vs moderate vs severe [according to the MASH-TAVI classification[14]], puncture height (at or above the centre of the femoral head vs below the centre of the femoral head), and access site puncture guidance (ultrasound vs angiographic guidance). Secondary endpoints included all-cause mortality; the individual endpoints of access-related major and minor vascular complications (VARC-3); bleeding events (VARC-3); vascular closure device failure according to VARC-3 – with the exception that the single use of a small plug-based VCD (Angio-Seal) after ProGlide use was not considered a VCD failure but part of the vascular closure strategy; and vascular stenting or vascular surgery due to VCD failure. Endpoints were evaluated based on the fulfilment of the individual VARC-3 criteria, without additional adjudication from the initial clinical event committees.

STATISTICAL ANALYSIS

All analyses were conducted following the intention-to-treat principle. The primary analyses were based on a one-stage meta-analysis. Binary clinical outcomes were assessed using a logistic regression model. Due to the anticipated low number of studies and patients, a less complex model with the trial as a dummy variable was initially prespecified. However, EuroIntervention required that we adjust the primary analysis to a model with stratified intercepts to account for baseline risk differences across trials.

Subgroup analysis was performed according to the previously mentioned, prespecified dichotomous or dichotomised baseline factors. The interpretation of these analyses was based on an interaction test, with a p-value<0.05 considered significant. Treatment effects were estimated as odds ratios (ORs) with their respective 95% confidence intervals (CIs) for each subgroup.

Continuous baseline variables such as age, body mass index, and femoral artery diameter were additionally assessed as continuous variables in logistic regression models with a treatment-by-baseline factor interaction. The predicted probability of the primary endpoint derived from these models was plotted over the range of the respective continuous baseline factor for each group.

As a secondary analysis, conventional two-stage meta-analyses were performed. Random-effects meta-analyses were conducted using the Mantel-Haenszel method with the Paule-Mandel estimator of between-study variance. Heterogeneity was assessed using Cochran's Q statistics and Higgins and Thompson's I^2. R, version 4.4.1 (R Foundation for Statistical Computing) was used for all statistical analyses.

REGISTRATION AND FUNDING SOURCE

This meta-analysis is registered with PROSPERO (CRD42022335295). There was no external funding source for this meta-analysis.

Results

INCLUDED STUDIES AND META-ANALYSIS POPULATION

Our search identified 871 records; after excluding duplicates and screening the titles, abstracts and full texts, four RCTs remained. One RCT was still recruiting and one RCT did not meet the inclusion criteria, and these were therefore excluded. The study selection process is outlined in **Figure 1**. The investigators of the two remaining RCTs agreed to

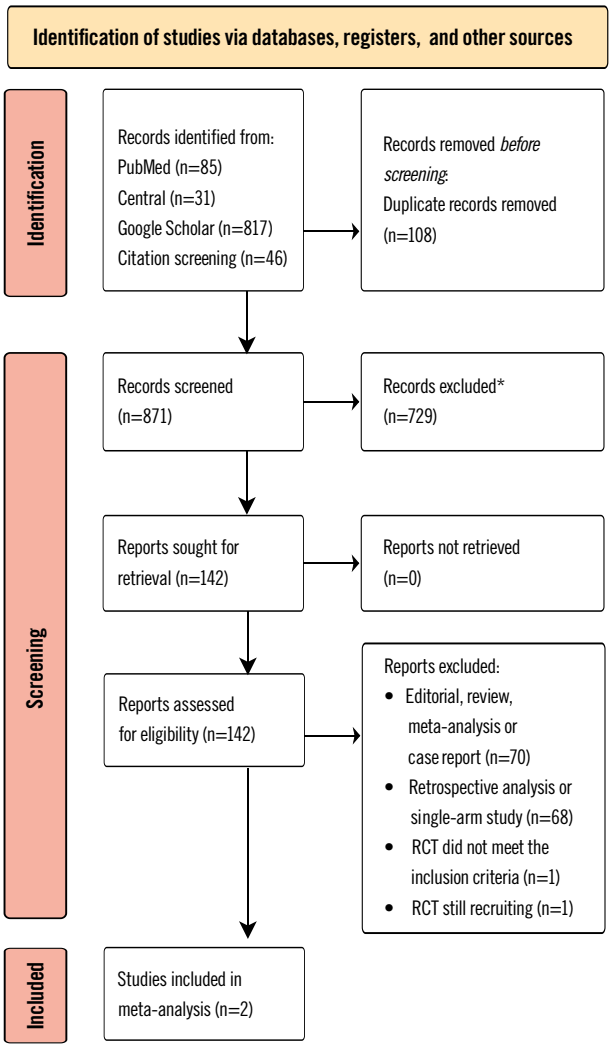

Figure 1. *PRISMA flowchart of trial identification and selection. *Different topic[33]. RCT: randomised controlled trial*

collaborate on a meta-analysis. Overall, the analysis included 362 patients treated with the ProGlide-based technique and 360 patients treated with the MANTA-based technique.

The main study design features are summarised in **Table 1**. Both RCTs compared one MANTA with two ProGlides for large-bore arteriotomy closure after transfemoral TAVI. In both studies, the two ProGlide VCDs were implanted in a rotated position relative to each other. One of the main differences between the two trials was the use of ultrasound. In the MASH-TAVI Trial, access site puncture procedures were exclusively performed under ultrasound guidance, while in the CHOICE-CLOSURE trial, the choice of puncture guidance technique was at the discretion of the operator. Additionally, in the CHOICE-CLOSURE trial, ultrasound assessments were conducted post-procedure to assess potential vascular complications, whereas the MASH-TAVI Trial relied solely on clinical follow-up for this purpose.

The ProGlide-based and MANTA-based technique groups were well balanced in terms of baseline characteristics, as illustrated in **Table 2**. Most patients in both groups were male (55.5% vs 54.4% in the ProGlide-based and MANTA-based technique groups, respectively) and elderly (81.0 [interquartile range {IQR} 76.0-84.0] vs 81.0 [IQR 77.0-84.0] years), at intermediate surgical risk as predicted by the Society of Thoracic Predicted Risk of Mortality score (3.2 [IQR 2.1-4.9] vs 3.1 [IQR 2.1-4.8]) and the presence of frailty and other comorbidities. Prediagnosed peripheral arterial disease was not common in either group (6.6% vs 6.7%), and vascular access site characteristics were similar **(Supplementary Table 3)**. The only noticeable difference was observed in the external iliac artery diameter, which was smaller in the ProGlide-based technique cohort compared to the MANTA-based technique cohort (7.0 [IQR 6.3-8.4] vs 8.0 [IQR 7.0-9.0] mm).

Vascular access was mostly guided by road mapping (52.1%) followed by ultrasound guidance (41.6%), with no difference between the suture-based and plug-based cohorts. The groups were largely comparable regarding main access sheath size, valve type, heparin and protamine use, as well as activated clotting time at vascular closure **(Supplementary Table 4)**. Short manual compression of less than 3 minutes was more common in the MANTA-based technique group (49.9% vs 80.3%), whereas compression of 3-10 minutes was more common in the ProGlide-based technique group (45.4% vs 13.2%) **(Table 3)**. The use of additional VCDs was exclusive

Table 1. Key design features of included trials.

	MASH-TAVI	CHOICE-CLOSURE
Identifier	NCT03811119	NCT04459208
Enrolment period	10/2018-01/2020	06/2020-06/2021
Multicentre study	Yes (2 centres)	Yes (3 centres)
Key inclusion criteria	Patient undergoing elective transfemoral TAVI with a commercially available device Common femoral artery diameter >5.0 mm (14-22 Fr compatible)	Patient undergoing elective transfemoral TAVI with a commercially available device
Key exclusion criteria	Vascular access site anatomy not suitable for percutaneous vascular closure with study VCDs Absence of preprocedural computed tomography data of the access site Morbidly obese or cachectic (BMI >40 kg/m^2 or <20 kg/m^2)	Vascular access site anatomy not suitable for percutaneous vascular closure with study VCDs Absence of preprocedural computed tomography data of the access site
Patients with MANTA/ProGlide VCD	102/104	258/258
Procedure	TAVI	TAVI
Used size of MANTA VCD	18 Fr	18 Fr
One or two ProGlide VCDs	2 ProGlides	2 ProGlides
Methods of vascular access	Ultrasound-guided	Angiography- or ultrasound-guided
Anticoagulation during procedure	UFH	UFH
Anticoagulation reversal	Protamine	Protamine
Primary endpoint	Access site-related major and minor vascular complications	Access site-related major and minor vascular complications
Outcome assessment	Clinical	Clinical and ultrasound
Vascular complications and bleeding definition	VARC-2	VARC-2
Vascular closure device failure definition	Failure of the vascular closure device to achieve haemostasis within 5 min or requiring additional endovascular manoeuvres (endovascular stenting, surgical techniques, or additional closure devices)	VARC-2
Follow-up	30 days	30 days

BMI: body mass index; Fr: French; TAVI: transcatheter aortic valve implantation; UFH: unfractionated heparin; VARC: Valve Academic Research Consortium; VCD: vascular closure device

Table 2. Baseline characteristics.

Variable	Total (n=722)	ProGlide-based technique (n=362)	MANTA-based technique (n=360)	*p*-value
Age, years	81.0 [76.0-84.0]	81.0 [76.0-84.0]	81.0 [77.0-84.0]	0.67
Male sex	397 (55.0)	201 (55.5)	196 (54.4)	0.83
Body mass index, kg/m^2	27.1 [24.4-30.8]	27.4 [24.0-31.0]	26.9 [24.6-30.5]	0.95
Logistic EuroSCORE I	2.9 [1.9-5.0]	3.0 [1.9-4.9]	2.9 [1.9-5.0]	0.60
STS-PROM score, %	3.1 [2.1-4.9]	3.2 [2.1-4.9]	3.05 [2.1-4.8]	0.66
Hypertension	616 (85.3)	310 (85.6)	306 (85.0)	0.89
Diabetes mellitus	248 (34.3)	126 (34.8)	122 (33.9)	0.86
Current smoker	56 (8.35)	29 (8.76)	27 (7.94)	0.81
Previous CABG	62 (8.6)	31 (8.6)	31 (8.6)	1.00
Previous PCI	192 (26.6)	93 (25.7)	99 (27.5)	0.64
Previous valve surgery	57 (7.9)	29 (8.0)	28 (7.8)	1.00
Previous stroke	102 (14.1)	46 (12.7)	56 (15.6)	0.33
Peripheral arterial disease	48 (6.7)	24 (6.6)	24 (6.7)	1.00
Atrial fibrillation	225 (31.2)	123 (34.0)	102 (28.3)	0.12
Baseline eGFR,	58.0 [43.0-73.0]	57.0 [43.0-70.0]	60.0 [43.8-76.2]	0.17
Baseline creatinine level, µmol/L	95.5 [75.0-120.0]	96.0 [75.0-120.0]	95.0 [74.0-120.0]	0.74
Baseline haemoglobin level, mmol/L	6.9 [6.1-7.7]	6.8 [6.0-7.7]	7.0 [6.1-7.7]	0.34
Baseline platelet count (10^9/l)	166 [135-205]	169 [132-207]	164 [137-202]	0.67
Antithrombotic therapy				
Oral anticoagulation	256 (35.8)	140 (39.3)	116 (32.3)	0.06
Antiplatelet therapy				0.29
None	351 (49.1)	180 (50.6)	171 (47.6)	
Aspirin	220 (30.8)	109 (30.6)	111 (30.9)	
Clopidogrel	59 (8.3)	33 (9.3)	26 (7.2)	
Other single antiplatelet therapy	2 (0.3)	1 (0.3)	1 (0.3)	
Dual antiplatelet therapy	83 (11.6)	33 (9.27)	50 (13.9)	

Values are median [interquartile range] or n (%). CABG: coronary artery bypass grafting; eGFR: estimated glomerular filtration rate; EuroSCORE: European System for Cardiac Operative Risk Evaluation; PCI: percutaneous coronary intervention; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality

to the ProGlide-based technique cohort, where they were needed in 50.0% of patients, with 45.0% of patients receiving an additional small plug as an adjunct to the suture-based vascular closure technique. The completeness of data, as well as distribution by trial for baseline characteristics, access site characteristics, procedural and vascular closure characteristics are shown in **Supplementary Table 5**-**Supplementary Table 8**.

PRIMARY AND SECONDARY ENDPOINTS

The primary endpoint of in-hospital main access site-related major and minor vascular complications was observed in 107 of 722 patients (14.8%); this was less common in the ProGlide-based technique group (40 of 362 patients [11.0%]) than in the MANTA-based technique group (67 of 360 patients [18.6%]; OR 0.54, 95% CI: 0.35-0.82) as depicted in the **Central illustration** and **Table 4**. These results were also consistent for the individual endpoints of access site-related major vascular complications (5 of 362 patients [1.4%] vs 14 of 360 patients [3.9%]; OR 0.35, 95% CI: 0.12-0.97) and access site-related minor vascular complications (35 of 362 patients [9.7%] vs 53 of 360 patients [14.7%]; OR 0.62, 95% CI: 0.39-0.98). The individual types of main access site vascular complications are illustrated in the **Central illustration**.

Overall, main access site-related bleeding events according to the VARC-3 definition were reported in 27 of 722 patients (3.7%) and were also significantly less common with the ProGlide-based technique (8 of 362 patients [2.2%] vs 19 of 360 patients [5.3%]; OR 0.41, 95% CI: 0.18-0.94). Type 2 and 3 bleeding events occurred numerically more frequently with the MANTA-based technique, but the difference between groups was not statistically significant **(Central illustration)**. There were no fatal bleeding events (type 4 bleeding), and only one type 1 bleeding event was adjudicated. In-hospital all-cause mortality was infrequent (10 of 722 patients [1.4%]), and there was no significant difference between the treatment groups (2 of 362 patients [0.6%] vs 8 of 360 patients [2.2%]; OR 0.24, 95% CI: 0.05-1.16). No patient died because of an access site-related vascular complication or an access site-related bleeding event. Among all 10 patients who died, only one patient had a bleeding complication, and one patient had a vascular closure device failure. A detailed description of all deceased patients and the respective cause of death is provided in **Supplementary Table 9**. Access site VCD failure according

Table 3. Vascular closure characteristics.

Variable	Total (n=722)	ProGlide-based technique (n=362)	MANTA-based technique (n=360)	*p*-value
Use of protamine				0.15
None	130 (18.1)	74 (20.4)	56 (15.6)	
Less than full dose	475 (66.0)	227 (62.7)	248 (69.3)	
Full dose	115 (16.0)	61 (16.9)	54 (15.1)	
Manual compression				<0.01
Less than 3 minutes	462 (65.1)	177 (49.9)	285 (80.3)	
Between 3 and 10 minutes	208 (29.3)	161 (45.4)	47 (13.2)	
More than 10 minutes	40 (5.6)	17 (4.8)	23 (6.5)	
Additional VCD	181 (25.1)	181 (50.0)	0 (0)	<0.01
Type of additional VCD				
MANTA	-	7 (1.9)	-	
ProGlide	-	11 (3.0)	-	
Small plug-based VCD	-	163 (45.0)	-	
Angio-Seal[a] 6 Fr	-	89 (24.6)	-	
Angio-Seal 8 Fr	-	71 (19.6)	-	
FemoSeal[a]	-	1 (0.3)	-	
ProGlide[b] and Angio-Seal	-	2 (0.6)	-	
Endovascular ballooning	50 (6.9)	16 (4.4)	34 (9.4)	0.01
Stent or stent graft	19 (2.6)	4 (1.1)	15 (4.2)	0.02
Unplanned vascular surgery	2 (0.3)	0 (0)	2 (0.6)	0.25

Values are n (%). [a]By Terumo; [b]by Abbott. Fr: French; VCD: vascular closure device

to VARC-3 was evenly distributed between both closure techniques (17 of 362 patients [4.7%] vs 18 of 360 patients [5.0%]; OR 0.94, 95% CI: 0.47-1.85), but vascular surgery or stenting due to VCD failure was more common with the MANTA-based technique (3 of 362 patients [0.8%] vs 13 of 360 patients [2.8%]; OR 0.22, 95% CI: 0.06-0.79).

SUBGROUP AND SENSITIVITY ANALYSES

Nearly all prespecified subgroups, with respect to the primary endpoint, consistently suggested a benefit of the ProGlide-based technique, without a statistically significant interaction **(Figure 2)**. Since only a few patients had a high femoral bifurcation above the femoral head, it is difficult to draw any conclusions about this subgroup. Analysis of continuous variables revealed a steady decline of the probability of the primary endpoint for the MANTA-based technique in larger femoral arteries **(Figure 3)**. A femoral artery diameter >9.5 mm was associated with a trend towards fewer major and minor access site-related vascular complications with the MANTA-based technique than with the ProGlide-based technique. All other interactions of continuous variables were in favour of the ProGlide-based technique **(Supplementary Figure 1, Supplementary Figure 2)**. The primary endpoint and the individual endpoint of access site-related minor vascular complications was significantly more common in the CHOICE-CLOSURE trial **(Supplementary Table 10)**.

Furthermore, we analysed the non-prespecified subgroups of compression duration and the additional use of a small plug-based VCD in the ProGlide cohort. We categorised the compression duration into three groups: less than 3 minutes, 3-10 minutes, and more than 10 minutes. A longer compression duration was associated with a higher likelihood of the primary endpoint (OR 3.55, 95% CI: 1.29-9.77). However, the used VCD did not significantly modify the effect of compression duration on the primary endpoint (OR 0.79, 95% CI: 0.39-1.64; p for interaction=0.53) **(Supplementary Figure 3)**.

The combination of two ProGlide VCDs with a small plug-based VCD demonstrated a significant reduction of the primary endpoint compared to the MANTA-based technique (OR 0.46, 95% CI: 0.26-0.82), whereas the pure ProGlide-based technique showed no significant difference compared to the MANTA-based technique (OR 0.61, 95% CI: 0.37-1.03).

The results of the different statistical models for the prespecified primary and secondary endpoints, as well as measurements for heterogeneity (I^2 and Tau) and model diagnostic parameters are summarised in **Supplementary Table 11**. There were no relevant outcome differences between the statistical models. Furthermore, the heterogeneity in the other statistical models was generally low.

Discussion

This is the first patient-level meta-analysis of RCTs comparing the ProGlide-based and MANTA-based techniques in patients with large-bore arterial access. The main findings of the study are as follows: (1) overall access site-related vascular complications were more common with the MANTA-based than with the ProGlide-based technique; (2) major access site complications were uncommon (<4%) but more frequent with the MANTA-based technique; (3) the MANTA-based

ProGlide- versus MANTA-based vascular closure technique for large-bore arterial access: a patient-level meta-analysis of two randomised trials including 722 patients.

Patient-level meta-analysis comparing MANTA and ProGlide vascular closure devices for large-bore vascular closure

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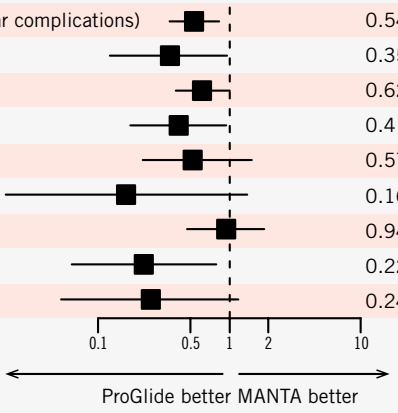
Outcome	OR (95% CI)	p
Primary endpoint (major & minor main access site-related vascular complications)	0.54 (0.35-0.82)	<0.01*
Major main access site-related vascular complications	0.35 (0.12-0.97)	0.04*
Minor main access site-related vascular complications	0.62 (0.39-0.98)	0.04*
Main access site-related bleeding event	0.41 (0.18-0.94)	0.04*
Main access site-related type 2 bleeding event	0.57 (0.22-1.47)	0.25
Main access site-related type 3 bleeding event	0.16 (0.02-1.36)	0.09
Vascular closure device failure	0.94 (0.47-1.85)	0.85
Stenting or vascular surgery due to VCD failure	0.22 (0.06-0.79)	0.02*
Death from any cause	0.24 (0.05-1.16)	0.08



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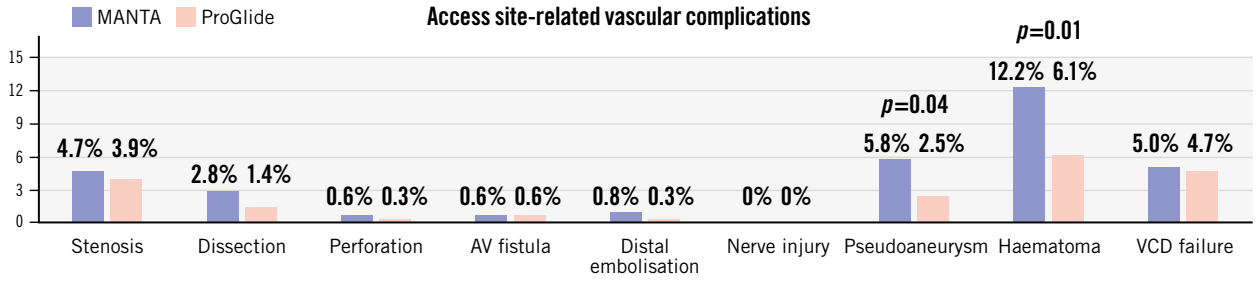

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*Outcome assessment according to Valve Academic Research Consortium-3 criteria. A) Primary and secondary endpoints. B) Details of access site-related vascular complications. *Indicates statistical significance. AV: arteriovenous; CI: confidence interval; OR: odds ratio; VCD: vascular closure device*

technique seemed to perform better in large femoral arteries (>9.5 mm); and (4) VCD failure was comparable between both groups – the MANTA-based technique required more covered stents or vascular surgery, while the ProGlide-based technique needed more additional VCDs.

Overall, vascular complication rates were lower than expected based on previous studies, especially with the suture-based technique[8,22,23]. This may be an effect of increasing operator experience, but it may also be related to the technical improvements of the latest TAVI generation. The recently published EASIER registry reported comparable low rates of major vascular complications with the new-generation TAVI devices[24].

Furthermore, it must be noted that the results of this individual patient-level meta-analysis differ from two previous study-level meta-analyses of RCT data[18,25]. Some endpoints, such as major access site-related vascular complications and major access site-related bleeding events, showed different significance levels. The harmonisation of endpoint definitions allowed us to change from VARC-2 to VARC-3. This patient-level meta-analysis employed a multilevel model with stratified intercepts, whereas the previous meta-analyses were study-level analyses.

One fundamental difference between the two vascular closure strategies is the fact that, in the ProGlide-based technique, wire access is maintained even after the sheath is removed and the sutures are tightened. This allows a wider and simpler variety of bailout strategies, such as additional VCDs. In this way, a suboptimal closure of the ProGlide VCD can be addressed directly and easily, whereas this is not possible with the MANTA VCD. In this meta-analysis, this advantage is reflected in the lower rate of vascular stenting or vascular surgery. The use of an additional small plug-based VCD after application of the ProGlide VCD has been established as part of the ProGlide-based technique[11,12] and was therefore not considered a VCD failure. In fact, the

Table 4. Numerical outcome of clinical endpoints.

Variable	Total (n=722)	ProGlide-based technique (n=362)	MANTA-based technique (n=360)
Primary endpoint (major and minor main access site-related vascular complications)	107 (14.8)	40 (11.0)	67 (18.6)
Major main access site-related vascular complications	19 (2.6)	5 (1.4)	14 (3.9)
Minor main access site-related vascular complications	88 (12.2)	35 (9.7)	53 (14.7)
Main access site-related bleeding	27 (3.7)	8 (2.2)	19 (5.3)
Type 1 bleeding	1 (0.1)	0 (0)	1 (0.3)
Type 2 bleeding	19 (2.6)	7 (1.9)	12 (3.3)
Type 3 bleeding	7 (1.0)	1 (0.3)	6 (1.7)
Type 4 bleeding	0 (0)	0 (0)	0 (0)
Need for blood transfusion			
None	652 (90.3)	327 (90.3)	325 (90.3)
1 unit	16 (2.2)	8 (2.2)	8 (2.2)
Between 2 and 4 units	46 (6.4)	24 (6.6)	22 (6.1)
More than 4 units	8 (1.1)	3 (0.8)	5 (1.4)
Vascular closure device failure	35 (4.9)	17 (4.7)	18 (5.0)
Stenting or vascular surgery due to VCD failure	16 (2.2)	3 (0.8)	13 (2.8)
Unplanned endovascular treatment (stent or balloon)	53 (7.3)	20 (5.5)	33 (9.2)
Acute kidney injury			
Stage 1	11 (1.5)	5 (1.4)	6 (1.7)
Stage 2	12 (1.7)	6 (1.7)	6 (1.7)
Stage 3	13 (1.8)	4 (1.1)	9 (2.5)
Need for renal replacement therapy	8 (1.1)	2 (0.6)	6 (1.7)
Stroke	16 (2.2)	6 (1.7)	10 (2.8)
Myocardial infarction	7 (1.0)	2 (0.6)	5 (1.4)
Death from any cause	10 (1.4)	2 (0.6)	8 (2.2)
Death from cardiovascular cause	7 (1.0)	1 (0.3)	6 (1.7)
Death from non-cardiovascular cause	3 (0.4)	1 (0.3)	2 (0.6)

Values are n (%). VCD: vascular closure device

non-prespecified subgroup analysis showed that this group achieved particularly favourable outcomes regarding the primary endpoint compared to the MANTA-based technique. These findings highlight the advantages of this hybrid vascular closure approach. In this context, the recently published randomised ACCESS-TAVI Trial, found significantly less vascular complications after TAVI when using a combination of one ProGlide and one Angio-Seal compared to vascular closure with two ProGlides[26].

The use of additional VCDs may also be the reason for the lower incidence of bleeding complications in the ProGlide-based technique group. Remarkably, short manual compression times (1-3 minutes) were more common in the MANTA-based group than in the ProGlide-based group but so were the number of haematomas, pseudoaneurysms, and overall access site bleeding events. The typically rapid, visually assessed haemostasis provided by the MANTA VCD could lead to an underestimation of residual bleeding or an underappreciation of VCD failure, potentially resulting in inappropriately short manual compression times. It is reasonable to assume a higher likelihood of subacute or clinically inapparent microbleeds within the MANTA-based technique treatment group. In contrast, the ProGlide VCD provides early warning of potential haemostatic problems, both during preclosure and during final suture tightening. However, in a subgroup analysis of compression duration, a higher incidence of the primary endpoint was observed with longer compression, regardless of the VCD used. It is plausible that a problematic vascular closure leads to longer compression. However, the extent to which compression duration influenced the results cannot be definitively determined.

Subgroup analysis suggests a consistent tendency of lower vascular complications with the ProGlide-based technique. Only patients with a large access site diameter (>9.5 mm) seemed to have similar complications with the MANTA-based technique. Previous retrospective studies have shown that vascular diameter is a predictor for vascular complications when using the MANTA-based technique[27,28]. It is possible that larger vessels promote better device deployment and adaptation.

Meticulous assessment and accurate puncture of the femoral arterial access site are essential elements for successful vascular closure. A growing body of evidence

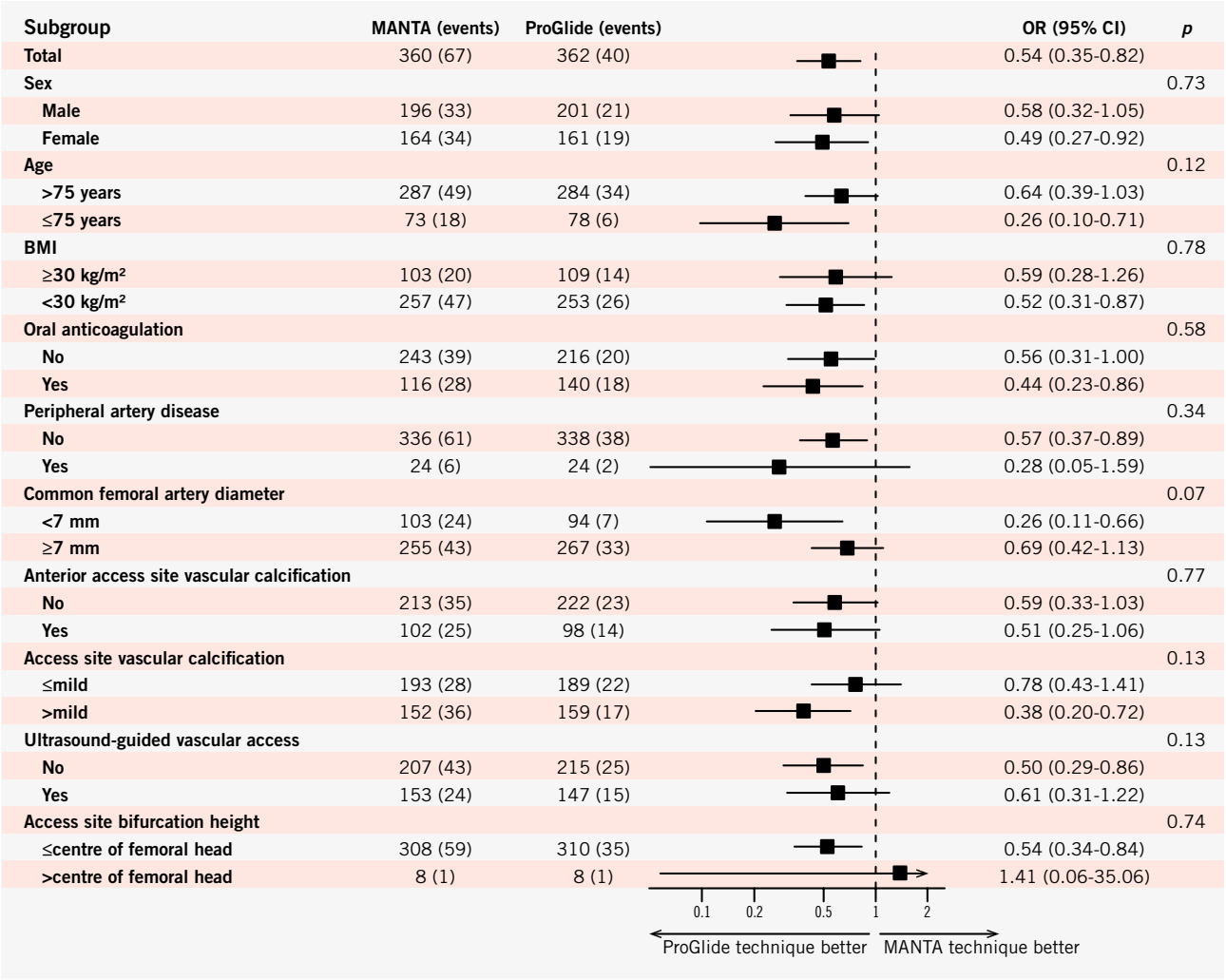

Figure 2. *Odds ratios for the primary endpoint in the intention-to-treat population in prespecified subgroups. BMI: body mass index; CI: confidence interval; OR: odds ratio*

suggests that ultrasound-guided puncture may be superior in this context[29]. However, the advantage of the ProGlide-based technique in this meta-analysis was independent of the method used for guiding arterial access. Moriyami et al observed a significant reduction in major vascular and bleeding complications in a retrospective study using ultrasound-guided MANTA VCD deployment[30]. A comparison of this strategy with the ProGlide-based technique has not been performed.

The ProStyle VCD (Abbott) was recently introduced as the successor to the ProGlide VCD. It features several design enhancements for improved handling, as well as stronger needles and an additional hydrophilic coating. Although the basic principles of suture-based VCD remain unchanged, the impact of these changes on VCD performance has not been adequately studied. A retrospective, non-randomised, propensity-matched analysis by Barbash et al found comparable rates of major and minor vascular complications between the new ProStyle and the MANTA-based technique[31]. Numerically, major vascular complications were more common with the ProStyle-based technique, which is an unexpected finding, given the minor improvements in the ProStyle's design.

Looking at the endpoints by trial, the MASH-TAVI study showed a significantly lower incidence of the primary endpoint, driven by a lower rate of minor access site vascular complications. In particular, haematomas and stenoses were more common in the CHOICE-CLOSURE trial[15]. A possible reason may be the exclusive use of ultrasound-guided puncture in the MASH-TAVI study. However, the subgroup analysis of our study showed no significant effect of the puncture technique on the outcomes. Another explanation for the higher rate of complications could be the significantly higher dose of heparin administered in the CHOICE-CLOSURE study. This was likely related to the higher body weight of the included patients and, therefore, had no significant effect on the activated clotting time at vascular closure. However, the most likely reason for the differences between the two trials is a detection bias. In the CHOICE-CLOSURE trial, an ultrasound examination of each access site was performed after the procedure, which revealed complications that may not have been seen on clinical examination. Since the current

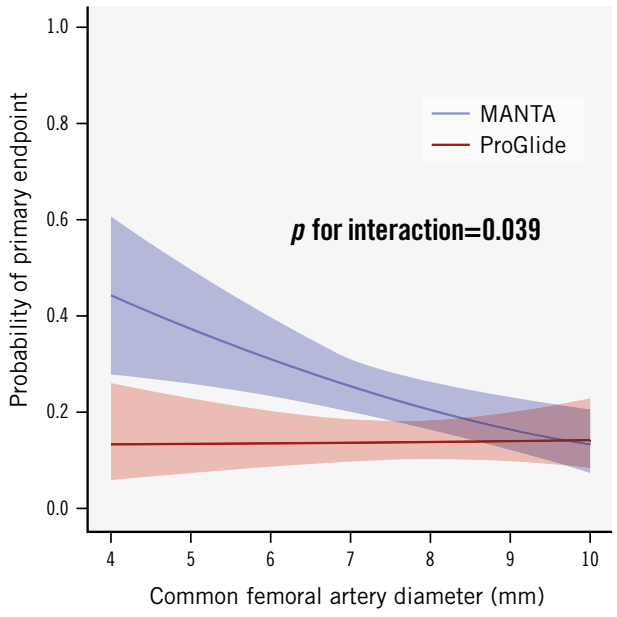

Figure 3. *Interaction of access site femoral artery diameter and the primary endpoint. Interaction is adjusted for the CHOICE-CLOSURE trial.*

VARC-3 criteria consider all findings (e.g., haematoma, vascular stenosis) related to the device insertion, delivery, and removal to be access site complications (regardless of clinical significance), the number of minor vascular complications is relatively higher than reported in the original publications[19]. To highlight these definition-related changes in the event numbers, we have displayed them in **Supplementary Figure 4**. Conversely, the number of minor bleeding events (type 1) was lower than in the original publications. This is because the new definition demands "a higher level of care or medical evaluation" (VARC-3) and no longer includes "any bleeding worthy of clinical mention" (VARC-2)[19,32]. Only one type 1 bleeding event was identified in our patient cohort under the VARC-3 criteria, whereas 47 events would have been recorded using the VARC-2 criteria. Moreover, it seems difficult to accurately document a higher level of care or medical evaluation in a study, as there are no specific parameters. This lack of precision may contribute to potential underreporting of type 1 bleeding events. It remains to be seen whether these small, but important, changes in the definitions will be reflected in the results of other studies as well. The higher rate of overall main access site-related bleeding in the MANTA-based technique group was thus mainly driven by severe (type 2) and life-threatening (type 3) bleeding events.

Overall, it is important to emphasise that the superior outcome of the ProGlide-based technique clearly extends to major bleeding and major vascular complications. The results are not solely attributable to minor events, which may be more variable than major complications due to detection bias or changed definitions. Therefore, further research is necessary to help identify patients who are vulnerable to complications with the MANTA-based technique. This would ensure an individual choice of closure technique for each patient.

Limitations

This meta-analysis has several limitations. First, the study only includes two RCTs and a relatively small number of patients. Second, as previously mentioned, the two trials differed with respect to access site guidance and access site follow-up. Third, only the 18 Fr MANTA VCD was used. Fourth, both trials only included patients receiving transfemoral TAVI. Other large-bore procedures, such as extracorporeal membrane oxygenation or endovascular aortic repair, are often characterised by a different clinical setting, and the results of this analysis may not be extended to these procedures. Furthermore, the weighting of clinically questionable minor vascular complications may also be a point of criticism in the comparison of the two devices. Finally, this meta-analysis only included the ProGlide VCD and not the new suture-based ProStyle VCD.

Conclusions

Main access site-related vascular complications and bleeding events are less common with the ProGlide-based technique than with the MANTA-based technique in this individual patient-level meta-analysis of two RCTs. The differences between both techniques in terms of main access site vascular complications are consistent among various subgroups. As the diameter of the femoral artery increases, outcomes with the plug-based technique improve.

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Conflict of interest statement

M. Abdel-Wahab reports that his hospital receives speaker honoraria and/or consultancy fees on his behalf from Medtronic and Boston Scientific. N. Van Mieghem received research grant support from Abbott, Boston Scientific, Edwards Lifesciences, Biotronik, Medtronic, Daiichi Sankyo, Abiomed, PulseCath BV, and Pie Medical Imaging. D. Tchétché received consultant fees from Abbott, Boston Scientific, Edwards Lifesciences, and Medtronic. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. PRISMA-IPD Checklist.
Supplementary Appendix 2. Electronic search strategies.
Supplementary Table 1. Trial quality and risk of bias of randomised trials according to Risk of Bias 2 tool.
Supplementary Table 2. Definition of major and minor main access site-related vascular complications (primary endpoint).
Supplementary Table 3. Computed tomography access site characteristics.
Supplementary Table 4. Procedural characteristics.
Supplementary Table 5. Baseline characteristics by trial.
Supplementary Table 6. Computed tomography access site characteristics by trial.
Supplementary Table 7. Procedural characteristics by trial.
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Supplementary Table 9. Causes of death.
Supplementary Table 10. Numerical outcome of clinical endpoints by trial.
Supplementary Table 11. Different statistical models for primary and secondary endpoints.
Supplementary Figure 1. Interaction of age and the primary endpoint.
Supplementary Figure 2. Interaction of BMI and the primary endpoint.
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Supplementary Figure 4. Effect of transposing outcomes from VARC-2 to VARC-3 on the number of primary endpoint events.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-25-00001

Supplementary data

Supplementary Appendix 1. PRISMA-IPD Checklist.

PRISMA-IPD section/topic	Item No	Checklist item	Reported on page
Title			
Title	1	Identify the report as a systematic review and meta-analysis of individual participant data.	1
Abstract			
Structured summary	2	Provide a structured summary including as applicable:	2 and 9
		Background: state research question and main objectives, with information on participants, interventions, comparators and outcomes.	
		Methods: report eligibility criteria; data sources including dates of last bibliographic search or elicitation, noting that IPD were sought; methods of assessing risk of bias.	
		Results: provide number and type of studies and participants identified and number (%) obtained; summary effect estimates for main outcomes (benefits and harms) with confidence intervals and measures of statistical heterogeneity. Describe the direction and size of summary effects in terms meaningful to those who would put findings into practice.	
		Discussion: state main strengths and limitations of the evidence, general interpretation of the results and any important implications.	
		Other: report primary funding source, registration number and registry name for the systematic review and IPD meta-analysis.	
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of the questions being addressed with reference, as applicable, to participants, interventions, comparisons, outcomes and study design (PICOS). Include any hypotheses that relate to particular types of participant-level subgroups.	5-6
Methods			
Protocol and registration	5	Indicate if a protocol exists and where it can be accessed. If available, provide registration information including registration number and registry name. Provide publication details, if applicable.	6,9
Eligibility criteria	6	Specify inclusion and exclusion criteria including those relating to participants, interventions, comparisons, outcomes, study design and characteristics (e.g. years when conducted, required minimum follow-up). Note whether these were applied at the study or individual level i.e. whether eligible participants were included (and ineligible participants excluded) from a study that included a wider population than specified by the review inclusion criteria. The rationale for criteria should be stated.	6-7, Table 1

Identifying studies - information sources	7	Describe all methods of identifying published and unpublished studies including, as applicable: which bibliographic databases were searched with dates of coverage; details of any hand searching including of conference proceedings; use of study registers and agency or company databases; contact with the original research team and experts in the field; open adverts and surveys. Give the date of last search or elicitation.	6-7, Suppl. page 5
Identifying studies - search	8	Present the full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl. page 6
Study selection processes	9	State the process for determining which studies were eligible for inclusion.	6-7, Figure 1
Data collection processes	10	Describe how IPD were requested, collected and managed, including any processes for querying and confirming data with investigators. If IPD were not sought from any eligible study, the reason for this should be stated (for each such study). If applicable, describe how any studies for which IPD were not available were dealt with. This should include whether, how and what aggregate data were sought or extracted from study reports and publications (such as extracting data independently in duplicate) and any processes for obtaining and confirming these data with investigators.	7
Data items	11	Describe how the information and variables to be collected were chosen. List and define all study level and participant level data that were sought, including baseline and follow-up information. If applicable, describe methods of standardising or translating variables within the IPD datasets to ensure common scales or measurements across studies.	7
IPD integrity	A1	Describe what aspects of IPD were subject to data checking (such as sequence generation, data consistency and completeness, baseline imbalance) and how this was done.	7
Risk of bias assessment in individual studies.	12	Describe methods used to assess risk of bias in the individual studies and whether this was applied separately for each outcome. If applicable, describe how findings of IPD checking were used to inform the assessment. Report if and how risk of bias assessment was used in any data synthesis.	7-9 and Suppl. Table 1
Specification of outcomes and effect measures	13	State all treatment comparisons of interests. State all outcomes addressed and define them in detail. State whether they were pre-specified for the review and, if applicable, whether they were primary/main or secondary/additional outcomes. Give the principal measures of effect (such as risk ratio, hazard ratio, difference in means) used for each outcome.	7-8
Synthesis methods	14	Describe the meta-analysis methods used to synthesis IPD. Specify any statistical methods and models used. Issues should include (but are not restricted to): • Use of a one-stage or two-stage approach. • How effect estimates were generated separately within each study and combined across studies (where applicable). • Specification of one-stage models (where applicable) including how clustering of patients within studies was accounted for. • Use of fixed or random effects models and any other model assumptions, such as proportional hazards. • How (summary) survival curves were generated (where applicable). • Methods for quantifying statistical heterogeneity (such as I^2 and τ^2). • How studies providing IPD and not providing IPD were analysed together (where applicable).	7-9

		• How missing data within the IPD were dealt with (where applicable).	
Exploration of variation in effects	A2	If applicable, describe any methods used to explore variation in effects by study or participant level characteristics (such as estimation of interactions between effect and covariates). State all participant-level characteristics that were analysed as potential effect modifiers, and whether these were pre-specified.	-
Risk of bias across studies	15	Specify any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to not obtaining IPD for particular studies, outcomes or other variables.	-
Additional analyses	16	Describe methods of any additional analyses, including sensitivity analyses. State which of these were pre-specified.	-
Results			
Study selection and IPD obtained	17	Give numbers of studies screened, assessed for eligibility, and included in the systematic review with reasons for exclusions at each stage. Indicate the number of studies and participants for which IPD were sought and for which IPD were obtained. For those studies where IPD were not available, give the numbers of studies and participants for which aggregate data were available. Report reasons for non-availability of IPD. Include a flow diagram.	9, Figure 1
Study characteristics	18	For each study, present information on key study and participant characteristics (such as description of interventions, numbers of participants, demographic data, unavailability of outcomes, funding source, and if applicable duration of follow-up). Provide (main) citations for each study. Where applicable, also report similar study characteristics for any studies not providing IPD.	Table 1
IPD integrity	A3	Report any important issues identified in checking IPD or state that there were none.	9
Risk of bias within studies	19	Present data on risk of bias assessments. If applicable, describe whether data checking led to the up-weighting or down-weighting of these assessments. Consider how any potential bias impacts on the robustness of meta-analysis conclusions.	Suppl. page 5
Results of individual studies	20	For each comparison and for each main outcome (benefit or harm), for each individual study report the number of eligible participants for which data were obtained and show simple summary data for each intervention group (including, where applicable, the number of events), effect estimates and confidence intervals. These may be tabulated or included on a forest plot.	Suppl. Table 11
Results of syntheses	21	Present summary effects for each meta-analysis undertaken, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified, and report the numbers of studies and participants and, where applicable, the number of events on which it is based.	9-11 Suppl. Table 7,10
		When exploring variation in effects due to patient or study characteristics, present summary interaction estimates for each characteristic examined, including confidence intervals and measures of statistical heterogeneity. State whether the analysis was pre-specified. State whether any interaction is consistent across trials.	
		Provide a description of the direction and size of effect in terms meaningful to those who would put findings into practice.	
Risk of bias across studies	22	Present results of any assessment of risk of bias relating to the accumulated body of evidence, including any pertaining to the availability and representativeness of available studies, outcomes or other variables.	Suppl. Table 1,

			Suppl. Table 10
Additional analyses	23	Give results of any additional analyses (e.g. sensitivity analyses). If applicable, this should also include any analyses that incorporate aggregate data for studies that do not have IPD. If applicable, summarize the main meta-analysis results following the inclusion or exclusion of studies for which IPD were not available.	-
Discussion			
Summary of evidence	24	Summarise the main findings, including the strength of evidence for each main outcome.	13
Strengths and limitations	25	Discuss any important strengths and limitations of the evidence including the benefits of access to IPD and any limitations arising from IPD that were not available.	14-18
Conclusions	26	Provide a general interpretation of the findings in the context of other evidence.	13-18
Implications	A4	Consider relevance to key groups (such as policy makers, service providers and service users). Consider implications for future research.	18
Funding			
Funding	27	Describe sources of funding and other support (such as supply of IPD), and the role in the systematic review of those providing such support.	9
Suppl. = Supplementary			

A1 – A3 denote new items that are additional to standard PRISMA items. A4 has been created as a result of re-arranging content of the standard PRISMA statement to suit the way that systematic review IPD meta-analyses are reported.

Supplementary Appendix 2. Electronic search strategies.

The following search strategies were applied for MEDLINE, CENTRAL, and GoogleScholar.

PUBMED

All fields

(vascular closure OR vascular closure device OR vascular access OR access OR vascular OR large-bore arteriotomy OR large bore arteriotomy OR large-bore arteriotomies OR large bore arteriotomies OR percutaneous closure OR percutaneous) AND (Manta OR plug-based OR plug based OR plug) AND (ProGlide OR Perclose OR suture-based OR suture based OR suture)

Filters: from 2016 – 2024

CENTRAL

#1 vascular closure or "vascular closure device" or "vascular access" or "access" or "vascular" or "large-bore arteriotomy" or "large bore arteriotomy" or "large-bore arteriotomies" or "large bore arteriotomies" or "percutaneous closure" or "percutaneous" (All text) (Word variations have been searched)

#2 AND Manta or "plug-based" or "plug based" or "plug" (All text) (Word variations have been searched)

#3 AND ProGlide or "Perclose" or "suture-based" or "suture based" or "suture" (All text) (Word variations have been searched)

Custom Range: 2016 - 2024

Google Scholar

vascular closure OR vascular closure device OR vascular access OR large bore arteriotomy OR large-bore arteriotomies OR percutaneous closure AND Manta OR plug-based OR plug based OR plug AND ProGlide OR Perclose OR suture-based OR suture based OR suture

Custom Range: 2016 - 2024

Supplementary Table 1. Trial quality and risk of bias of randomised trials according to Risk of Bias 2 tool.

Trials (Ref. #)	Randomisation process	Deviation from intended interventions	Missing outcome data	Measurement of outcome	Selection of reported results	Overall
CHOICE-CLOSURE	low	some concerns	low	low	low	Some concerns
MASH	low	some concerns	some concerns	some concerns	low	Some concerns

Supplementary Table 2. Definition of major and minor main access site-related vascular complications (primary endpoint).

Vascular and access-related complications = defined as any complication related to the device insertion, delivery, and complete removal of all its components (delivery catheter, sheath, guide wire), excluding the actual implantation in the heart.
Main access site = is defined as the access route through which the delivery device of the transcatheter heart valve is introduced.
Major vascular complication One of the following: ▪ Aortic dissection or aortic rupture ▪ Vascular (arterial or venous) injury (perforation, rupture, dissection, stenosis, ischaemia, arterial or venous thrombosis including pulmonary embolism, arteriovenous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, infection) or compartment syndrome resulting in death, VARC type ≥ 2 bleeding†, limb or visceral ischaemia, or irreversible neurologic impairment ▪ Distal embolization (non-cerebral) from a vascular source resulting in death, amputation, ▪ limb or visceral ischaemia, or irreversible end-organ damage ▪ Unplanned endovascular or surgical intervention resulting in death, VARC type ≥ 2 bleeding†, limb or visceral ischaemia, or irreversible neurologic impairment ▪ Closure device failure* resulting in death, VARC type ≥ 2 bleeding†, limb or visceral ischaemia, or irreversible neurologic impairment
Minor vascular complication One of the following: ▪ Vascular (arterial or venous) injury (perforation, rupture, dissection, stenosis, ischemia, arterial or venous thrombosis including pulmonary embolism, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, infection) not resulting in death, VARC type ≥ 2 bleeding†, limb or visceral ischemia, or irreversible neurologic impairment ▪ Distal embolization treated with embolectomy and/or thrombectomy, not resulting in death, amputation, limb or visceral ischemia, or irreversible end-organ damage ▪ Any unplanned endovascular or surgical intervention, ultra-sound guided compression, or thrombin injection, not resulting in death, VARC type ≥ 2 bleeding†, limb or visceral ischemia, or irreversible neurologic impairment ▪ Closure device failure*
† According to Valve Academic Research Consortium-3 definition * Defined as failure to achieve hemostasis at the access site, resulting in alternative treatment (other than manual compression or planned adjunctive endovascular balloon inflation). The use of a small plug-based vascular closure device (AngioSeal) on top of a suture-based device was not considered closure device failure. TAVI = Transcatheter aortic valve implantation.

Supplementary Table 3. Computed tomography access site characteristics.

Variable	Total (n=722)	ProGlide-based technique (n=362)	MANTA-based technique (n=360)	p-value
Diameter of iliofemoral arteries (access-site)				
Common iliac (mm)	9.3 ± 2.1	9.3 ± 2.1	9.4 ± 2.2	0.24
External iliac (mm)	7.4 [7.0-9.0]	7.0 [6.3-8.4]	8.0 [7.0-9.0]	0.03
Common femoral (mm)	7.6 [6.6-8.8]	7.5 [6.7-8.6]	7.8 [6.5-9.0]	0.81
Common femoral diameter smaller than 7mm	197 (27.4%)	103 (28.5%)	94 (26.3%)	0.49
Calcification of iliofemoral artery (access-site) †				0.81
None	139 (20.1%)	65 (18.7%)	74 (21.4%)	
Mild	243 (35.1%)	124 (35.6%)	119 (34.5%)	
Moderate	222 (32.0%)	112 (32.2%)	110 (31.9%)	
Severe	89 (12.8%)	47 (13.5%)	42 (12.2%)	
Anterior vascular calcification of the access site	200 (31.5%)	98 (30.6%)	102 (32.4%)	0.70
Height of the common femoral bifurcation (access-site) ‡				0.79
Grade 1	337 (53.2%)	175 (55.0%)	162 (51.3%)	
Grade 2	104 (16.4%)	52 (16.4%)	52 (16.5%)	
Grade 3	149 (23.5%)	70 (22.0%)	79 (25.0%)	
Grade 4	28 (4.4%)	13 (4.1%)	15 (4.8%)	
Grade 5	12 (1.9%)	5 (1.6%)	7 (2.2%)	
Grade 6	4 (0.6%)	3 (0.9%)	1 (0.3%)	

Values are mean ± SD or median [interquartile range] or no (%).
† None: no calcification; (B) mild: ≤1 cm, ≤180º; (C) moderate: >1 cm, ≤180º; severe: >180º.
‡ Bifurcation height was graded as follows: grade 1, below the inferior border of the femoral head; grade 2, at the inferior border of the femoral head; grade 3, below the center of the femoral head but above the inferior border of the femoral head; grade 4, at the center of the femoral head; grade 5, above the center of the femoral head; grade 6, above or at the superior border of the femoral head.

Supplementary Table 4. Procedural characteristics.

Variable	Total (n=722)	ProGlide-based technique (n=362)	MANTA-based technique (n=360)	p-value
Main access site = right femoral artery	629 (87.1%)	312 (86.2%)	317 (88.1%)	0.52
Mean sheath size (French)	14.0 [14.0-16.0]	14.0 [14.0-16.0]	14.0 [14.0-16.0]	0.62
Access site puncture guidance				
Ultrasound	300 (41.6%)	147 (40.6%)	153 (42.5%)	0.66
Road mapping	376 (52.1%)	194 (53.6%)	182 (50.6%)	0.46
Regular angiography	45 (6.2%)	21 (5.8%)	24 (6.7%)	0.74
Valve type				0.75
Evolut R	121 (16.8%)	62 (17.1%)	59 (16.4%)	
Evolut PRO	232 (32.1%)	112 (30.9%)	120 (33.3%)	
Sapien 3	244 (33.8%)	122 (33.7%)	122 (33.9%)	
ACURATE neo	82 (11.4%)	41 (11.3%)	41 (11.4%)	
Lotus	40 (5.5%)	23 (6.4%)	17 (4.7%)	
Allegra	2 (0.3%)	2 (0.6%)	0 (0.0%)	
JenaValve	1 (0.1%)	0 (0.0%)	1 (0.3%)	
Depth of puncture in the MANTA group (cm)	-	-	5.0 [4.0-5.5]	
Heparin dose (IU)	8947 ± 3090	8923 ± 3205	8971 ± 2974	0.83
ACT at vascular closure (seconds)	178 ± 43.7	178 ± 45.4	179 ± 42.1	0.63

Values are mean ± SD or median [interquartile range] or no (%).
ACT = Activated clotting time, IU = international units.

Supplementary Table 5. Baseline characteristics by trial.

Variable	CHOICE-CLOSURE (n=516)	MASH (n=206)	Number of missing values	p-value
Age (years)	81.0 [77.0-84.0]	81.0 [75.0-84.8]	0	0.89
Male sex	286 (55.4%)	111 (53.9%)	0	0.77
Body mass index (kg/m²)	27.6 [24.7-31.2]	26.2 [23.6-29.3]	0	<0.01
Logistic EuroSCORE I	3.10 [2.02-5.35]	2.54 [1.69-3.82]	0	<0.01
Society of Thoracic Surgeons score (%)	3.27 [2.2-5.1]	2.71 [1.7-4.0]	1	<0.01
Hypertension	470 (91.1%)	146 (70.9%)	0	<0.01
Diabetes mellitus	201 (39.0%)	47 (22.8%)	0	<0.01
Current Smoking	47 (9.1%)	9 (5.8%)	51	0.26
Coronary artery disease				0.07
Previous CABG	46 (8.9%)	16 (7.8%)	1	0.74
Previous PCI	123 (23.8%)	69 (33.5%)	0	0.01
Previous valve surgery	49 (9.5%)	8 (3.9%)	0	0.02
Previous stroke	66 (12.8%)	36 (17.6%)	1	0.12
Peripheral vascular disease	39 (7.6%)	9 (4.4%)	0	0.17
Atrial fibrillation	163 (31.6%)	62 (30.1%)	0	0.76
Baseline eGFR	57.0 [42.0-72.2]	60.0 [46.0-78.0]	1	0.10
Baseline creatinine level (µmol/l)	96.0 [77.0-119]	94.0 [77.0-111]	1	0.10
Baseline hemoglobin level (mmol/l)	6.8 [6.1-7.7]	7.00 [6.1-7.7]	2	0.51
Antithrombotic therapy				
Oral anticoagulation	96 (38.5%)	60 (29.1%)	7	0.02
Antiplatelet therapy			7	<0.01
None	268 (52.7%)	83 (40.3%)		
Aspirin	164 (32.2%)	56 (27.2%)		
Clopidogrel	39 (7.7%)	20 (9.7%)		
Other single antiplatelet therapy	2 (0.4%)	0 (0.0%)		
Dual antiplatelet therapy	36 (7.1%)	47 (22.8%)		

Values are median [interquartile range] or no (%).
CABG = coronary artery bypass grafting, eGFR = estimated glomerular filtration rate, PCI = percutaneous coronary intervention, STS = Society of Thoracic Surgeons.

Supplementary Table 6. Computed tomography access site characteristics by trial.

Variable	CHOICE-CLOSURE (n=516)	MASH (n=206)	Number of missing values	p-value
Diameter of iliofemoral arteries (access-site)				
Common iliac (mm)	9.6 ± 2.2	8.5 ± 1.7	79	<0.01
External iliac (mm)	8.0 [7.0-9.0]	6.7 [6.0-7.7]	78	<0.01
Common femoral (mm)	8.0 [7.0-9.0]	7.0 [6.1-7.9]	3	<0.01
Common femoral diameter smaller than 7 mm	103 (19.0%)	94 (45.9%)	3	<0.01
Calcification of iliofemoral artery (access-site) †			29	0.13
None	88 (17.9%)	51 (25.2%)		
Mild	173 (35.2%)	70 (34.7%)		
Moderate	162 (33.0%)	60 (29.7%)		
Severe	68 (13.8%)	21 (10.4%)		
Anterior vascular calcification of the access-site	163 (33.2%)	37 (25.7%)	87	0.11
Height of the common femoral bifurcation (access-site) ‡			88	0.89
Grade 1	260 (53.1%)	77 (53.5%)		
Grade 2	77 (15.7%)	27 (18.8%)		
Grade 3	117 (23.9%)	32 (22.2%)		
Grade 4	23 (4.7%)	5 (3.5%)		
Grade 5	9 (1.8%)	3 (2.1%)		
Grade 6	4 (0.8%)	0 (0.0%)		

Values are mean ± SD or median [interquartile range] or no (%).
*Vessel tortuosity was graded on the following scale: grade 0, no tortuosity; grade 1, mild tortuosity (30°-60°); grade 2, moderate tortuosity (60° to 90°); and grade 3 severe tortuosity (≥90°).
† None: no calcification; (B) mild: ≤1 cm, ≤180º; (C) moderate: >1 cm, ≤180º; severe: >180º.
‡ Bifurcation height was graded as follows: grade 1, below the inferior border of the femoral head; grade 2, at the inferior border of the femoral head; grade 3, below the center of the femoral head but above the inferior border of the femoral head; grade 4, at the center of the femoral head; grade 5, above the center of the femoral head; grade 6, above or at the superior border of the femoral head.

Supplementary Table 7. Procedural characteristics by trial.

Variable	CHOICE-CLOSURE (n=516)	MASH (n=206)	Number of missing values	p-value
Main access site = right femoral artery	454 (88.0%)	175 (85.0%)	0	0.33
Mean sheath size (French)	14.0 [14.0-16.0]	16.0 [14.0-16.0]	0	<0.01
Access site puncture guidance				
Ultrasound	94 (18.2%)	206 (100.0%)	0	<0.01
Road mapping	376 (72.9%)	0 (0.0%)	0	<0.01
Regular angiography	45 (8.7%)	0 (0.0%)	0	<0.01
Valve type			0	<0.01
Evolut R	85 (16.5%)	36 (17.5%)		
Evolut PRO	158 (30.6%)	74 (35.9%)		
Sapien 3	176 (34.1%)	68 (33.0%)		
ACURATE neo	73 (14.1%)	9 (4.4%)		
Lotus	22 (4.3%)	18 (8.7%)		
Allegra	2 (0.4%)	0 (0.0%)		
Jena Valve	0 (0.0%)	1 (0.5%)		
Depth of puncture in the Manta group (cm)	4.50 [4.0-5.5]	5.00 [4.5-5.5]	0	0.01
Heparin dose (IU)	10233 ± 2437	5726 ± 2020	0	<0.01
ACT at vascular closure (seconds)	179 (42.1)	178 (45.4)	0	0.63

Values are mean ± SD or median [interquartile range] or no (%).
ACT = Activated clotting time.

Supplementary Table 8. Vascular closure characteristics by trial.

Variable	CHOICE-CLOSURE (n=516)	MASH (n=206)	Number of missing values	p-value
Use of protamine			2	<0.01
None	0 (0.0%)	130 (63.1%)		
Less than full dose	399 (77.6%)	76 (36.9%)		
Full dose	115 (22.4%)	0 (0.00%)		
Manual compression			12	<0.01
Less than 3 minutes	271 (53.8%)	191 (92.7%)		
Between 3-10 minutes	199 (39.5%)	9 (4.37%)		
More than 10 minutes	34 (6.75%)	6 (2.91%)		
Additional VCD	151 (29.3%)	38 (18.5%)	0	<0.01
Type of additional VCD			0	<0.01
MANTA	6 (1.2%)	1 (0.5%)		
ProGlide	3 (0.6%)	8 (3.9%)		
Angio-Seal 6Fr	84 (16.3%)	5 (2.4%)		
Angio-Seal 8Fr	51 (9.9%)	20 (9.7%)		
Femoseal	1 (0.2%)	0 (0.0%)		
ProGlide and Angio-Seal	0 (0.0%)	2 (1.0%)		
Endovascular ballooning	34 (6.6%)	16 (7.8%)	0	0.69
Stent or stent-graft	15 (2.9%)	4 (1.9%)	0	0.64
Unplanned vascular surgery	0 (0.0%)	2 (1.0%)	0	0.20
Values are no (%). Fr = French; VCD = Vascular closure device.				

Supplementary Table 9. Causes of death.

Patient ID	Date of TAVI	Date of death	Cardiovascular death	Procedure related bleeding or vascular complication	Cause of death
9	11.07.2020	23.07.2020	No	No	Sepsis of unknown origin
271	22.10.2020	26.10.2020	Yes	No	Right-sided heart failure and possible pulmonary embolism during surgery for femur fracture after fall
282	27.10.2020	28.10.2020	Yes	No	Cardiogenic shock after thrombotic coronary occlusion
289	30.10.2020	07.11.2020	Yes	No	Stroke with subsequent aspiration pneumonia
306	06.11.2020	12.11.2020	No	Type 2 bleeding and hematoma	Respiratory failure due to pneumonia and chronic lung fibrosis
465	26.02.2021	13.03.2021	Yes	No	Mixed shock after aspiration and intrathoracic bleeding caused by short resuscitation because of 3rd degree heart block
476	24.06.2021	29.06.2021	Yes	No	Spontaneous intracerebral bleeding under aspirin monotherapy
503	21.04.2021	04.05.2021	No	No	Therapy de-escalation during sepsis with acute kidney injury with need for dialysis
564	21.02.2019	22.02.2019	Yes	No	Cardiogenic shock after coronary obstruction during TAVI
641	19.09.2019	14.10.2019	Yes	Vascular closure device failure	New severe MR after TAVI and decision for MTEER, pericardial effusion and cardiac arrest after MTEER

MR = Mitral regurgitation, MTEER = Mitral transcatheter edge-to-edge repair, TAVI = Transcatheter aortic valve implantation

Supplementary Table 10. Numerical outcome of clinical endpoints by trial.

Variable	CHOICE-CLOSURE (n=516)	MASH (n=206)	Number of missing values	p-value
Primary endpoint (major and minor main access site related vascular complications)	93 (18.0%)	14 (6.8%)	0	<0.01
Major main access site related vascular complications	17 (3.3%)	2 (1.0%)	0	0.13
Minor main access site related vascular complications	76 (14.7%)	12 (5.8%)	0	0.01
Access site dissection	10 (1.9%)	5 (2.4%)		0.77
Access site stenosis	30 (5.8%)	1 (0.5%)		<0.01
Access site perforation	2 (0.4%)	1 (0.5%)		1.00
Access site AV-fistula	3 (0.6%)	1 (0.5%)		1.00
Access site pseudoaneurysm	25 (4.8%)	5 (2.4%)		0.21
Access site hematoma	64 (12.4%)	2 (1.0%)		<0.01
Access site neve injury	0 (0%)	0 (0%)		-
Access site distal embolization	4 (0.8%)	0 (0.0%)		0.58
Main access site related bleeding	21 (4.1%)	6 (2.9%)	0	
Type 1 bleeding	1 (0.2%)	0 (0.0%)		1.00
Type 2 bleeding	16 (3.1%)	3 (1.5%)		0.30
Type 3 bleeding	4 (0.8%)	3 (1.5%)		0.41
Type 4 bleeding	0 (0.0%)	0 (0.0%)		-
Need for blood transfusion			0	0.99
None	466 (90.3%)	186 (90.3%)		
One unit	11 (2.1%)	5 (2.4%)		
Between 2-4 units	33 (6.4%)	13 (6.3%)		
More than 4 units	6 (1.2%)	2 (1.0%)		
Vascular closure device failure*	27 (5.2%)	8 (3.9%)	0	0.57
Stenting or vascular surgery due to VCD failure	11 (2.1%)	5 (2.4%)	0	0.81
Unplanned endovascular treatment (stent or balloon)	45 (8.7%)	8 (3.9%)	0	0.04
Acute kidney injury			1	0.08
None	485 (94.0%)	200 (97.6%)		
Stage 1	9 (1.7%)	2 (1.0%)		
Stage 2	9 (1.7%)	3 (1.5%)		
Stage 3	13 (2.5%)	0 (0.0%)		
Need for renal replacement	8 (1.6%)	0 (0.0%)	0	0.11
Stroke	10 (1.9%)	6 (2.9%)	0	0.60
Myocardial infarction	3 (0.6%)	4 (1.9%)	0	0.21

Death from any cause	8 (1.6%)	2 (1.0%)	0	0.73
Death from cardiovascular cause	5 (1.0%)	2 (1.0%)	0	1.00
Death from non-cardiovascular cause	3 (0.6%)	0 (0.0%)	0	0.56
Values are no (%). VARC = Valve Academic Research Consortium. * according to VARC-3.				

Supplementary Table 11. Different statistical models for primary and secondary endpoints.

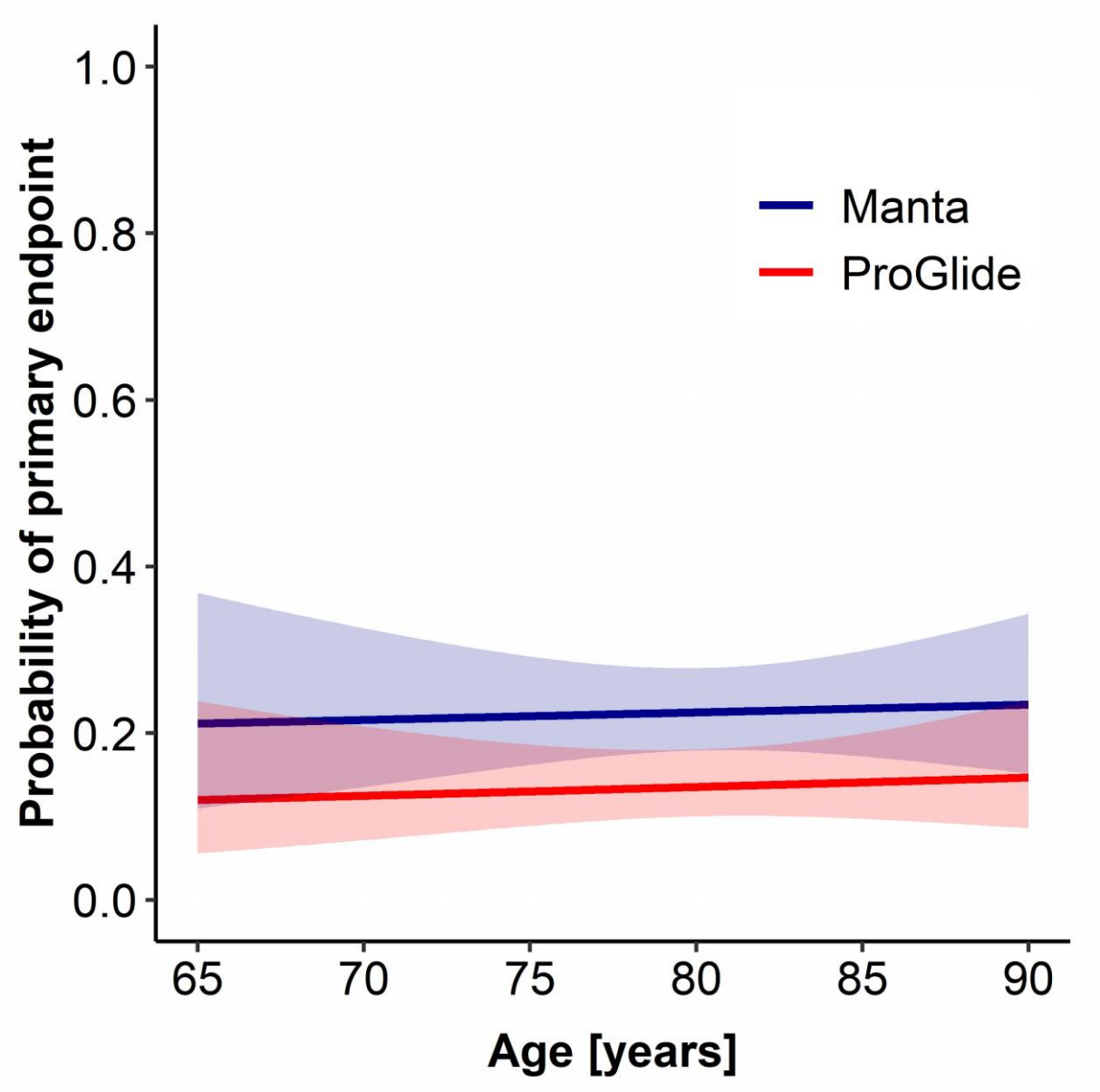
Statistical model	Odds ratio (95%confidence interval)	p-value	Tau²	I²	isSingular	AIC	BIC	logLik	Deviance	r2m	r2c
Primary endpoint (major and minor main access site related vascular complications)											
One-stage logistic regression with stratified intercepts	0.54 (0.35-0.82)	<0.01	-	-	-	586.83	600.58	-290.42	580.83	-	-
Pooled analysis by logistic regression with trial as covariate	0.54 (0.35-0.82)	<0.01	-	-	-	586.83	600.58	-290.42	580.83	-	-
Multilevel model with random intercepts	0.54 (0.35-0.82)	<0.01	0.27	0.08	no	593.43	607.18	-293.72	581.09	0.03	0.01
Multilevel model with random intercepts and slopes	0.47 (0.24-0.92)	0.03	0.04	0.06	yes	593.43	607.18	-293.72	581.09	0.03	0.01
Two-stage random effects model	0.60 (0.42-0.86)	<0.01	-	0.00	-	-	-	-	-	-	-
Two-stage fixed effects model	0.60 (0.42-0.85)	<0.01	-	0.00	-	-	-	-	-	-	-
Major main access site related vascular complications											
One-stage logistic regression with stratified intercepts	0.35 (0.12-0.97)	0.04	-	-	-	173.4	187.15	-83.7	167.4	-	-
Pooled analysis by logistic regression with trial as covariate	0.35 (0.12-0.97)	0.04	-	-	-	173.4	187.15	-83.7	167.4	-	-
Multilevel model with random intercepts	0.35 (0.12-0.97)	0.04	0.08	0.02	no	176.98	190.72	-85.49	169.1	0.08	0.01
Multilevel model with random intercepts and slopes	0.27 (0.04-1.64)	0.16	0.16	0.03	yes	176.98	190.72	-85.49	169.1	0.08	0.01
Two-stage random effects model	0.39 (0.15-1.02)	0.06	-	0.00	-	-	-	-	-	-	-

Two-stage fixed effects model	0.38 (0.14-1.00)	0.05	-	0.00	-	-	-	-	-	-	-
Minor main access site related vascular complications											
One-stage logistic regression with stratified intercepts	0.62 (0.39-0.98)	0.04	-	-	-	524.53	538.27	-259.26	518.53	-	-
Pooled analysis by logistic regression with trial as covariate	0.62 (0.39-0.98)	0.04	-	-	-	524.53	538.27	-259.26	518.53	-	-
Multilevel model with random intercepts	0.62 (0.39-0.97)	0.04	0.22	0.22	no	530.53	544.28	-262.27	518.87	0.02	0.01
Multilevel model with random intercepts and slopes	0.57 (0.29-1.08)	0.09	0.02	0.17	yes	530.53	544.28	-262.27	518.87	0.02	0.01
Two-stage random effects model	0.66 (0.44-0.99)	0.04	-	0.00	-	-	-	-	-	-	-
Two-stage fixed effects model	0.66 (0.44-0.98)	0.04	-	0.00	-	-	-	-	-	-	-
Main access site related bleeding											
One-stage logistic regression with stratified intercepts	0.41 (0.18-0.94)	0.04	-	-	-	231.02	244.76	-112.51	225.02	-	-
Pooled analysis by logistic regression with trial as covariate	0.41 (0.18-0.94)	0.04	-	-	-	231.02	244.76	-112.51	225.02	-	-
Multilevel model with random intercepts	0.41 (0.18-0.94)	0.04	0.00	0.00	no	231.58	245.33	-112.79	225.58	0.06	0.01
Multilevel model with random intercepts and slope	0.41 (0.18-0.94)	0.04	0.00	0.00	no	231.58	245.33	-112.79	225.58	0.06	0.01
Two-stage random effects model	0.42 (0.19-0.95)	0.04	-	0.00	-	-	-	-	-	-	-
Two-stage fixed effects model	0.42 (0.19-0.95)	0.04	-	0.00	-	-	-	-	-	-	-
Main access site related type 2 bleeding											

One-stage logistic regression with stratified intercepts	0.57 (0.22-1.47)	0.25	-	-	-	178.6	192.34	-86.3	172.6	-	-
Pooled analysis by logistic regression with trial as covariate	0.57 (0.22-1.47)	0.25	-	-	-	178.6	192.34	-86.3	172.6	-	-
Multilevel model with random intercepts	0.57 (0.22-1.47)	0.25	0.00	0.00	yes	180.33	194.07	-87.16	174.33	0.02	<0.01
Multilevel model with random intercepts and slopes	0.57 (0.22-1.47)	0.25	0.00	0.00	yes	180.33	194.07	-87.16	174.33	0.02	<0.01
Two-stage random effects model	0.63 (0.19-2.05)	0.15	-	0.19	-	-	-	-	-	-	-
Two-stage fixed effects model	0.58 (0.23-1.46)	0.14	-	0.19	-	-	-	-	-	-	-
Main access site related type 3 bleeding											
One-stage logistic regression with stratified intercepts	0.16 (0.02-1.36)	0.09	-	-	-	80.14	93.88	-37.07	74.14	-	-
Pooled analysis by logistic regression with trial as covariate	0.16 (0.02-1.36)	0.09	-	-	-	80.14	93.88	-37.07	74.14	-	-
Multilevel model with random intercepts	0.16 (0.02-1.36)	0.09	0.00	0.00	yes	80.81	94.56	-37.41	74.81	0.20	0.01
Multilevel model with random intercepts and slopes	0.16 (0.02-1.36)	0.09	0.00	0.00	yes	80.81	94.56	-37.41	74.81	0.20	0.01
Two-stage random effects model	0.24 (0.04-1.45)	0.12	-	0.00	-	-	-	-	-	-	-
Two-stage fixed effects model	0.23 (0.04-1.34)	0.10	-	0.00	-	-	-	-	-	-	-
Vascular closure device failure											
One-stage logistic regression with stratified intercepts	0.94 (0.47-1.85)	0.85	-	-	-	285.96	299.71	-139.98	279.96	-	-

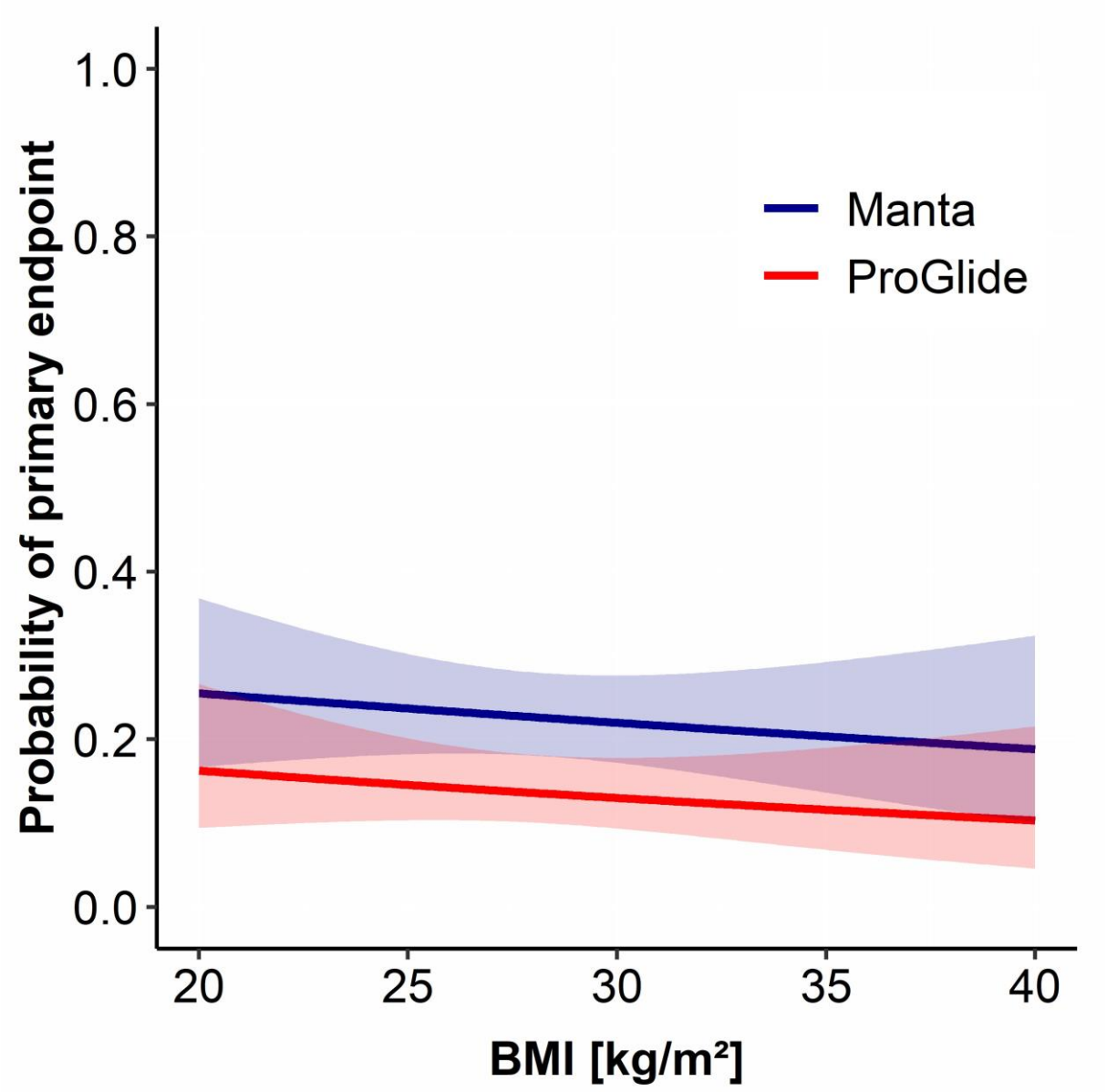
Pooled analysis by logistic regression with trial as covariate	0.94 (0.47-1.85)	0.85	-	-	-	285.96	299.71	-139.98	279.96	-	-
Multilevel model with random intercepts	0.94 (0.47-1.85)	0.85	0.00	0.00	yes	286.11	299.85	-140.05	280.11	0.00	0.00
Multilevel model with random intercepts and slopes	0.94 (0.47-1.85)	0.85	0.00	0.00	yes	286.11	299.85	-140.05	280.11	0.00	0.00
Two-stage random effects model	0.92 (0.43-1.96)	0.82	-	0.06	-	-	-	-	-	-	-
Two-stage fixed effects model	0.94 (0.49-1.79)	0.85	-	0.06	-	-	-	-	-	-	-
Stenting or vascular surgery due to VCD failure											
One-stage logistic regression with stratified intercepts	0.22 (0.06-0.79)	0.02	-	-	-	152.54	166.29	-73.27	146.54	-	-
Pooled analysis by logistic regression with trial as covariate	0.22 (0.06-0.79)	0.02	-	-	-	152.54	166.29	-73.27	146.54	-	-
Multilevel model with random intercepts	0.22 (0.06-0.79)	0.02	0.00	0.00	yes	152.61	166.35	-73.3	146.61	0.15	0.01
Multilevel model with random intercepts and slopes	0.22 (0.06-0.79)	0.02	0.00	0.00	yes	152.61	166.35	-73.3	146.61	0.15	0.01
Two-stage random effects model	0.29 (0.09-0.97)	0.04	-	0.00	-	-	-	-	-	-	-
Two-stage fixed effects model	0.26 (0.08-0.83)	0.02	-	0.00	-	-	-	-	-	-	-
Death from any cause											
One-stage logistic regression with stratified intercepts	0.24 (0.05-1.16)	0.08	-	-	-	107.13	120.88	-50.57	101.13	-	-
Pooled analysis by logistic regression with trial as covariate	0.24 (0.05-1.16)	0.08	-	-	-	107.13	120.88	-50.57	101.13	-	-

Multilevel model with random intercepts	0.24 (0.05-1.16)	0.08	0.00	0.00	yes	107.51	121.26	-50.76	101.51	0.13	0.01
Multilevel model with random intercepts and slopes	0.24 (0.05-1.16)	0.08	0.00	0.00	yes	107.51	121.26	-50.76	101.51	0.13	0.01
Two-stage random effects model	0.30 (0.07-1.21)	0.09	-	0.00	-	-	-	-	-	-	-
Two-stage fixed effects model	0.29 (0.07-1.19)	0.09	-	0.00	-	-	-	-	-	-	-
AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, logLik = Log-Likelihood, r2m = Marginal R^2, r2c = Conditional R^2.											



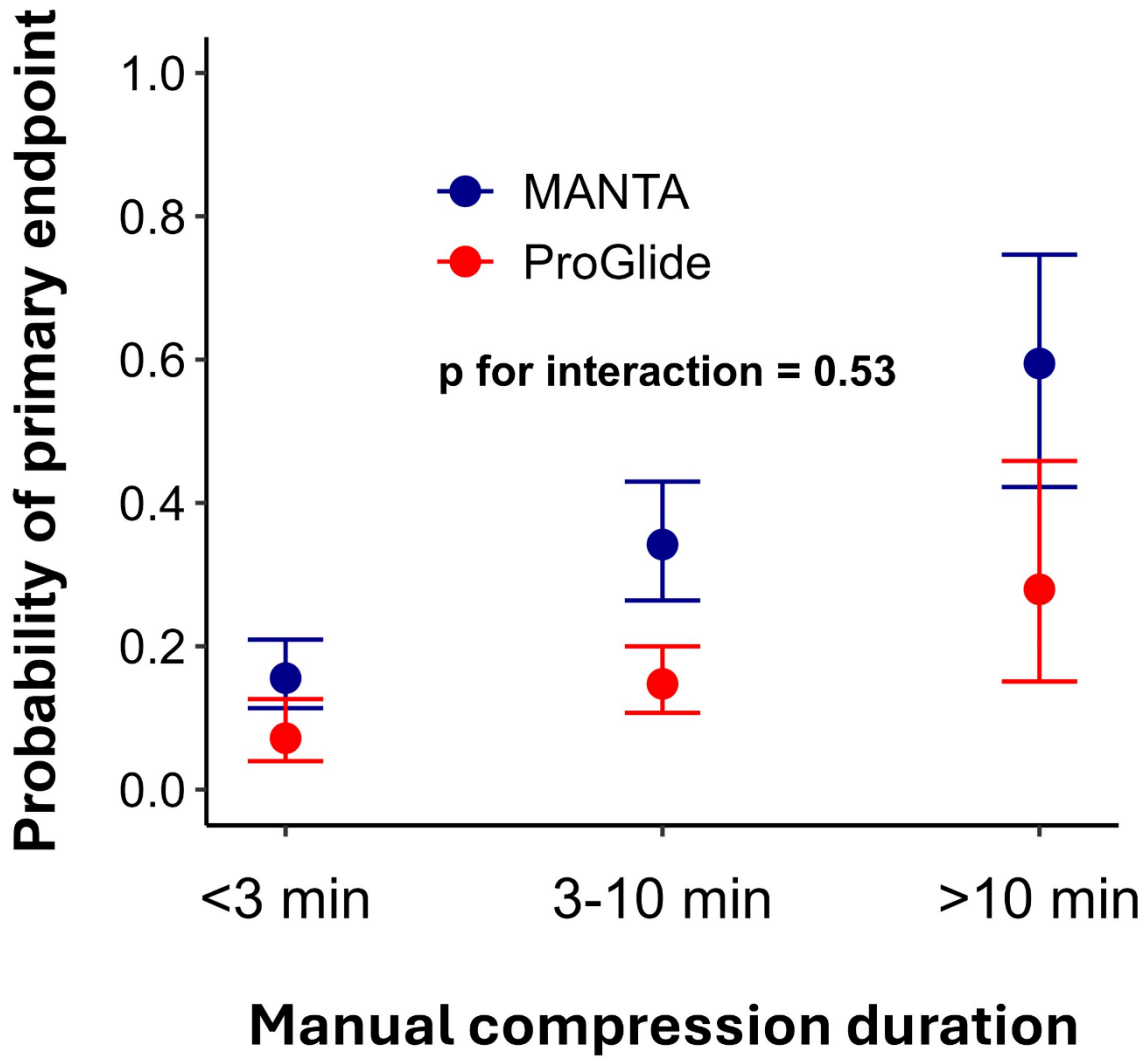
Supplementary Figure 1. Interaction of age and the primary endpoint.

Interaction is adjusted for the CHOICE-CLOSURE trial.



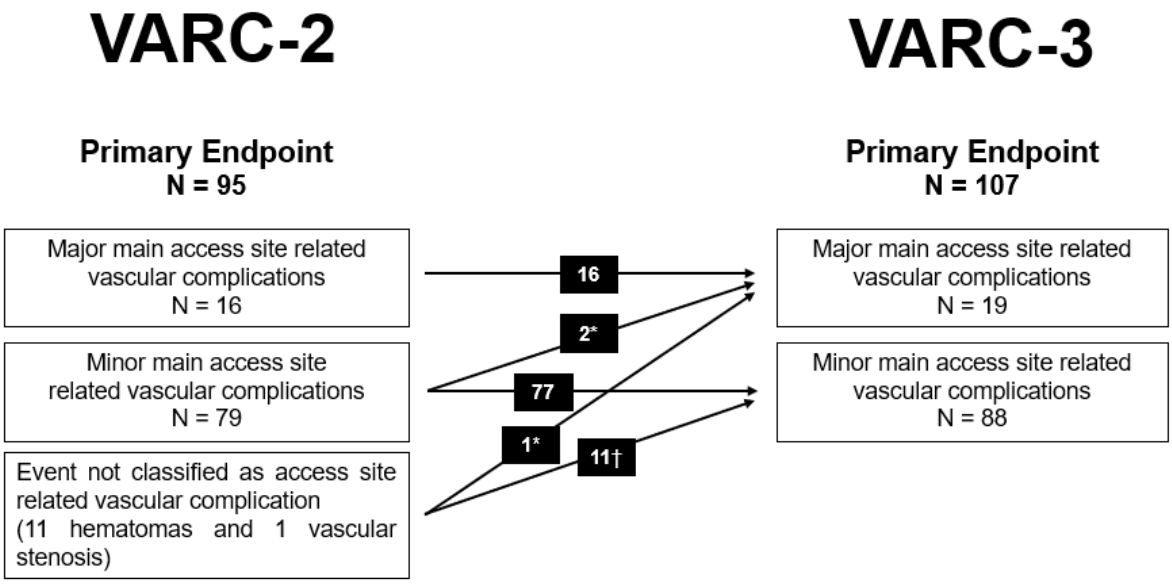
Supplementary Figure 2. Interaction of BMI and the primary endpoint.

Interaction is adjusted for the CHOICE-CLOSURE trial. BMI = body mass index.



Supplementary Figure 3. Interaction of manual compression duration and the primary endpoint.

Interaction is adjusted for the CHOICE-CLOSURE trial.



Supplementary Figure 4. Effect of transposing outcomes from VARC-2 to VARC-3 on the number of primary endpoint events.

VARC = Valve Academic Research Consortium.

*Access site hematoma and overt type 2 bleeding event. These were previously not evaluated as overt access site related bleeding. According to VARC-3, any procedural blood loss should be considered overt bleeding. The CHOICE-CLOSURE event committee did not consider a procedural related blood loss through the delivery sheath as a bleeding event.

† According to VARC-3 any complication related to the device insertion, delivery, and complete removal of all its components (delivery catheter, sheath, guide wire) should be considered as an access-related complication. The CHOICE-CLOSURE event committee did not consider hematomas that were associated with a significant bleeding event as a vascular complication.