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Research Paper

Extravascular compared to Intravascular Femoral Closure is Associated with Less Bleeding and Similar MACE after Percutaneous Coronary Intervention

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Abstract

Background: Various types of vascular closure devices (VCDs) are frequently utilized in patients undergoing percutaneous coronary intervention (PCI) in order to prevent arterial access site bleeding, which represents one of the most relevant complications associated with adverse clinical outcomes. This study aims to compare directly two mechanistically different types of femoral closure (FC) devices in patients undergoing PCI.

Methods: This single-center, prospective, observational study includes consecutively patients either treated by the extravascular StarClose SE® (Abbott, Illinois, U.S.A.) or the intravascular AngioSeal™ FC (St. Jude Medical, Inc., St. Paul, MN, U.S.A.) after PCI. The primary endpoint was bleeding complications, the secondary endpoint was major adverse cardiac events (MACE) at 30 days of follow-up.

Results: 200 patients in each group (StarClose SE® and AngioSeal™) were enrolled following PCI. The rates of overall and non-access site bleedings were significantly higher in the AngioSeal™ group (56%; 6%) compared to the StarClose SE® group (43.5%; 0.5%) (p = 0.012; 0.003). Additionally, complicated access site bleedings were also significantly higher in the AngioSeal™ group (p = 0.011). No significant differences of MACE were observed in both groups. However, there was a higher rate of unsuccessful implantation of the StarClose SE® (n=12, excluded from the study).

Conclusions: In case of successful implantation**,** FC by the AngioSeal™ is associated with the higher rate of both access and non-access site bleedings, but similar rates of MACE at 30 days compared to the StarClose SE® device.

Key words: percutaneous coronary intervention, transfemoral access, transradial access, femoral closure, vascular closure devices

Introduction

Arterial access site bleeding is considered to be one of the most relevant complications associated with adverse clinical outcomes in patients undergoing percutaneous coronary intervention (PCI) [1]. A recent meta-analysis revealed a significantly increased risk of periprocedural mortality in patients undergoing PCI with concomitant access site bleeding (risk ratio [RR] 1.71, 95% confidence interval [CI] 1.37 - 2.13) [2].

Recently, due to its advantage of reduced access site bleeding a transradial access (TRA) is regarded as the preferred approach for PCI [3, 4]. Campelo-Parada

et al. demonstrated a significantly lower rate of long-term major adverse cardiac events (MACE) in patients undergoing PCI using TRA compared to those with transfemoral access (TFA) [5]. Nonetheless, TFA still remains the most commonly used approach because of several potential drawbacks of TRA, e.g., higher frequency of crossover to alternative vascular access, longer procedure time, inability to insert mechanical circulatory support devices, and risk for potential arterial conduits for bypass graft surgery [6].

To improve the efficiency of hemostasis, especially following femoral PCI vascular closure devices (VCD) were developed continuously over the last decades, although manual compression and sequential application of pressure bandages is often used [7]. Numerous prior trials demonstrated that the application of VCD being based on collagen plug, clip, or suture mechanisms might significantly decrease femoral access site bleeding in patients undergoing diagnostic cardiac catheterization as well as PCI compared to conventional manual compression [8, 9]. Furthermore, Chodor et al. revealed no significant benefit of TRA in access site bleeding compared to TFA with consecutive use of StarClose SE® for femoral closure (FC) in patients with ST segment elevation myocardial infarction (STEMI) [10].

However, direct comparisons between various VCDs in terms of their efficacy in the interventional settings have been rarely investigated. Therefore, this study aims to compare directly one specific intravascular FC device (AngioSeal™, St. Jude Medical, Inc., St. Paul, MN, U.S.A.) with one specific extravascular FC device (StarClose SE®, Abbott, Illinois, U.S.A.) in patients after PCI focusing on overall and access site bleedings as well as MACE at short-term follow-up.

Methods

Study population

The present study was conducted as a single-center, prospective, nonrandomized study being performed at the First Department of Medicine, University Medical Centre Mannheim (UMM) in Mannheim, Germany. The study was designed as an open-label, observational all-comers study in order to recruit a consecutively generalizable and representative study population comparable to the daily practice in other PCI centers. The study was carried out according to the principles of the Declaration of Helsinki and was approved by the medical ethics commission II of the Medical Faculty Mannheim, University of Heidelberg, Germany. Written informed consent was obtained from all participating patients or their legal representatives.

Patients being planned for PCI were screened at our cardiologic department and included consecutively to this study, when they were subsequently treated either with intravascular closure device (AngioSeal™) or with extravascular closure device (StarClose SE®) after femoral PCI. Patients being treated with other VCD than AngioSeal™ or StarClose SE® after PCI were excluded. Patients with unsuccessful implantation of the AngioSeal™ or the StarClose SE® device immediately after PCI in the catherization laboratory were excluded. Further inclusion and exclusion criteria accorded to criteria of "The Femoral Closure versus Radial Compression Devices Related to Percutaneous Coronary Interventions" (FERARI, clinicaltrials.gov identifier: NCT02455661) study being outlined in detail in the previously published method paper [11]. According to an estimation of the power using the data of the first 100 patients, a sample size of 200 patients in each group was necessary to power the study sufficiently for the primary endpoint. Therefore, 200 consecutive patients were recruited in both groups [11].

Procedure

Conduction of PCI procedure (i.e., choice of access site, sheath diameter, used technique and PCI materials) was not influenced by the study protocol and based on the operator's discretion. Procedures with switching of access site were excluded. Heparin was used to achieve an activated clotting time (ACT) of 250-300 s during PCI and ACT was measured frequently. Peri-interventional additional antithrombotic treatment (i.e., bivalirudin or abciximab) as well as post-interventional loading with antiplatelet therapy were carried out according to European guidelines [12].

Femoral closure (FC) was achieved using the AngioSeal™ or the StarClose SE® device applied by experienced interventional cardiologists (≥100 applications each). Following the FC, a conventional pressure band was located in a standard fashion around the hips for 6 h. Subsequently, these patients were checked for peripheral perfusion, motor function and sensibility regularly.

The Angio-Seal™ is composed of an absorbable polymer anchor compressing the inner vascular wall and an absorbable collagen sponge compressing the outer vascular wall. According to the instructions of use, an insertion sheath and an arteriotomy locator are snapped together and positioned with an introducer right in the femoral artery noticeable of the blood reflow. After removing the insertion sheath and introducer, the Angio-Seal™ device is inserted through the locator. A clicking sound indicates that the anchor has left the sheath. Pulling back the device,

the anchor was pressed against the inner vessel wall and further retreat released the collagen plug in the exterior puncture hole. After removing the whole components of the device, a suture tube appeared. Applying pressure downward and meanwhile pulling back the device hub, the collagen compacts the outer vessel wall. A black mark is released, which should be cut close to the skin [11].

The StarClose SE® contains an introducer sheath, dilator, guidewire, and clip applier with a star shaped nitinol clip. When the primary procedure is completed, the catheter is removed and the sheath is left in place or exchanged for a StarClose SE® compatible sheath. The clip applier is attached to the introducer sheath, signaled by a loud click to the operator. A button on the device is depressed to expand the flexible wings in the artery and provide the user a tactile signal of being against the anterior femoral artery. The device is applied with light traction against the arteriotomy, then a "no tension" position while stabilizing the device is assumed. A sliding element on the body of the device is then advanced, splitting the sheath as the clip is advanced to the arteriotomy. The operator is signaled the completion of the sheath splitting by another loud click. While pressing down with the device, a trigger button is depressed to deploy the clip. Subsequently, the clip applier and introducer sheath are withdrawn. The nitinol clip provides a secure extravascular closure that does not invade the vessel lumen [13].

Data acquisition

Baseline characteristics, past medical history including chronic kidney (glomerular filtration rate <60ml/min) or liver disease, heart failure (according to left ventricular ejection fraction) as well as laboratory values (i.e. creatinine, hemoglobin, platelet count and International Normalized Ratio (INR)) were collected from the in-hospital documentation system. All patients were followed up during hospital stay and until 30 days after the index procedure directly and by standardized telephone visits.

Definition of study endpoints

The primary endpoint was defined by the overall rate of all relevant access site and non-access site bleedings within 30 days following PCI. Overall bleedings were classified according to established criteria such as the "Bleeding Academic Research Consortium" (BARC), "The Thrombolysis in Myocardial Infarction" (TIMI), and "The Global Use of Strategies to Open Occluded Arteries" (GUSTO) [14-16]. Access site complications were defined as hematomas, active bleedings, dissections, pseudoaneurysms, arteriovenous fistulae, and retroperitoneal hematomas [17]. Access site bleedings were classified according to the FERARI classification [11].

The secondary endpoint consisted of MACE within 30 days of follow-up, which comprised all-cause and cardiovascular death, myocardial infarction, stent thrombosis, target lesion revascularization (TLR) as well as target vessel revascularization (TVR).

Statistical analysis

Statistical analysis was performed using SPSS Statistics (IBM, Armonk, NY) and GraphPad Prism (GraphPad Software, Inc., La Jolla, CA). Data are presented as medians with interquartile ranges (25^{th} to 75^{th} percentiles) or as total numbers with group-related percentages. The p-values < 0.05 were considered statistically significant, p-values < 0.01 were considered as a statistical trend. Normal distribution of data was tested with the Kolmogorov-Smirnov test. For data with normal distribution, the Student t test was applied. Categorical variables were compared using the Chi-squared test; in case of low event rates the Fischer's exact test was applied. Baseline characteristics, which were shown to differ significantly between the two groups, were adjusted using uni- and multivariate logistic regression analyses for the predefined study endpoints.

Results

Baseline characteristics

A total of 400 consecutive patients after PCI were enrolled in the present study. 200 patients were treated with the intravascular device AngioSeal™ and another 200 patients were treated with the extravascular device StarClose SE® following PCI.

In a total of 16 patients of the StarClose SE® group the implantation of the device was unsuccessful bedside in the cardiac catheterization laboratory (12 patients: technical failure, device unable to fix at the outer vessel site; 4 patients: insufficient closure with relevant unstoppable arterial bleeding directly after release). These 16 patients received additional application of the FemoStop™ (Abbott, Illinois, U.S.A) to ensure final hemostasis and were excluded from final analysis.

Table 1 displays the baseline characteristics between the AngioSeal™ and the StarClose SE® group. The AngioSeal™ was significantly more often performed in patients with stable angina pectoris (p = 0.0001) or with a positive viability testing (p = 0.0004), whereas the StarClose SE® was more often used in patients with STEMI (p = 0.0001) or in angiographic control examinations (p = 0.015). Patients in the

AngioSeal™ group suffered more often from peripheral vascular disease and underwent more often surgery of coronary artery bypass grafting (CABG). The rate of AngioSeal™ application was significantly higher in patients undergoing PCI with 5F sheath diameter (p = 0.001), whereas the StarClose SE® was more often performed in patients undergoing PCI with 6F sheath diameter (p = 0.009). No significant differences of preexisting antiplatelet or anticoagulation therapy before PCI between both groups were observed except for acetylsalicylic acid (ASA) (73% for StarClose SE® group and 56% for the AngioSeal™ group, p = 0.002) and low molecular weight heparin (LMWH) (1 patient in the StarClose SE® group and 10 patients in the AngioSeal™ group, p = 0.011) **(Table 2)**.

Table 1. Baseline characteristics of PCI patients with application of vascular closure devices

	All (n=400)	StarClose (n=200)	AngioSeal (n=200)	p value*
Male, n (%)	286 (71.5)	151 (75.5)	135 (67.5)	0.077
Age, years (IQR)	68 (59-78)	67 (57-77)	71 (61-78)	**0.045**
Height, cm (IQR)	172 (165-178)	172 (165-178)	171 (165-178)	0.242
Weight, kg (IQR)	81 (70-91)	81 (70-90)	81 (72-92)	0.377
BMI, kg/m² (IQR)	27 (24-30)	27 (24-30)	28 (24-31)	0.128
Indication, n (%)				
Stable AP	55 (13.8)	5 (2.5)	50 (25)	**0.0001**
Unstable AP	65 (16.3)	30 (15)	35 (17.5)	0.498
NSTEMI	107 (26.8)	60 (30)	47 (23.5)	0.142
STEMI	59 (14.8)	46 (23)	13 (6.5)	**0.0001**
Pos. viability testing	12 (3)	1 (0.5)	11 (5.5)	**0.0004**
Angio. Control	75 (18.8)	47 (23.5)	28 (14)	**0.015**
Arrhythmia	9 (2.3)	4 (2)	5 (2.5)	1.000
Syncope	7 (1.8)	2 (1)	5(2.5)	0.449
Heart failure	9 (2.3)	3 (1.5)	6 (3)	0.503
Others	2 (0.5)	2 (1)	0 (0)	0.499
Cardiovascular risk factors, n (%)				
Arterial Hypertension	302 (75.5)	147 (73.5)	155 (77.5)	0.352
Diabetes mellitus	129 (32.3)	61 (30.5)	68 (34)	0.454
Smoking, each *n* (%)				
Active	103 (25.8)	67 (33.5)	36 (18)	**0.0004**
Past	66 (16.5)	28 (14)	38 (19)	0.178
Dyslipidemia	162 (40.5)	77 (38.5)	85 (42.5)	0.415
Cardiac family history	80 (20)	47 (23.5)	33 (16.3)	0.080
Prior medical history, n(%)				
Coronary artery disease	196 (49)	95 (47.5)	101 (50.5)	0.548
CABG	31 (7.8)	9 (4.5)	22 (11)	**0.015**
Peripher vascular disease	21 (5.3)	6 (3)	15 (7.5)	**0.044**
Stroke/TIA	24 (6)	10 (5)	14 (7)	0.400
Heart valve surgery	6 (1.5)	2 (1)	4 (2)	0.685
Atrial fibrillation, each				
Paroxymal	27 (6.8)	17 (8.5)	10 (5)	0.163
Persistent	5 (1.3)	3 (1.5)	2(1)	1.000
Permanent	11 (2.8)	6 (3)	5 (2.5)	1.000
Non classified	9 (2.3)	0 (0)	9 (4.5)	**0.004**
Pacemaker	15 (3.8)	7 (3.5)	8 (4)	0.792
Implantable defibrillator	13 (3.3)	6 (3)	7 (3.5)	0.778
Impaired liver function	1 (0.3)	0 (0)	1 (0.5)	1.000
Prior GI bleeding	8 (2)	5 (2.5)	3 (1.5)	0.475
LVEF, % (median, IQR)	45 (39-55)	50 (44-57)	44 (30-50)	**0.001**
Baseline laboratory values (median, IQR)				
Hb, g/dl	13.8 (12.6-14.8)	14.0 (13.0-14.9)	13.7 (12.1-14.7)	**0.038**
Serum creatinine, mg/dl	1.01 (0.82-1.20)	0.98 (0.81-1.15)	1.05 (0.84-1.25)	**0.026**
Thrombocytes, 10^9/l	220 (182-263)	222 (187-266)	212 (179-261)	0.296
INR	1.01 (0.97-1.06)	1.01 (0.98-1.07)	1.01 (0.96-1.06)	0.175
Sheath diameter, n (%)				
5 French	39 (9.8)	10 (5)	29 (14.5)	**0.001**
6 French	358 (89.5)	187 (93.5)	171 (85.5)	**0.009**
7 French	3 (0.8)	3 (1.5)	(0)	0.248
Hospital stay, days (IQR)	7 (3-10)	7 (4-9)	7 (2-11)	0.498

BMI body mass index, *CABG* coronary artery bypass grafting, *GI* gastrointestinal, *Hb* hemoglobin, *INR* International Normalized Ratio, *LVEF* left ventricular ejection fraction, *(N)STEMI* (non) ST-segment elevation myocardial infarction, *TIA* transient ischaemic attack.

* p values for the comparison of femoral closure by StarClose versus femoral closure by AngioSeal group, significant p values are in bold type ($p < 0.05$)

Table 2. Antithrombotic therapies being used in the study

	All (n=400)	StarClose (n=200)	AngioSeal (n=200)	p value*
Prior antithrombotic treatment, *n* (%)				
ASA	263 (65.8)	146 (73)	117 (58.5)	**0.002**
Clopidogrel	66 (16.6)	31 (15.5)	35 (17.7)	0.590
Prasugrel	12 (3)	3 (1.5)	9 (4.5)	0.139
Ticagrelor	7 (1.8)	5 (2.5)	2 (1)	0.449
Prior oral anticoagulation, *n* (%)				
Phenprocoumon	29 (7.3)	15 (7.5)	14 (7)	0.847
Rivaroxaban	8 (2)	3 (1.5)	5 (2.5)	0.724
Dabigatran	6 (1.5)	3 (1.5)	3 (1.5)	1.000
Apixaban	4 (1)	1 (0.5)	3 (1.5)	0.623
LMWH	11 (2.8)	1 (0.5)	10 (5)	**0.011**
Antithrombotic Loading therapy during PCI, n (%)				
ASA	7 (1.8)	0 (0)	7 (3.5)	**0.015**
Clopidogrel	203 (50.7)	83 (41.5)	120 (60)	**0.0002**
Prasugrel	41 (10.3)	27 (13.5)	14 (7)	**0.032**
Ticagrelor	52 (13)	50 (25)	2 (1)	**0.0001**
ASA + clopidogrel	46 (11.5)	21 (10.5)	25 (12.5)	0.531
ASA + prasugrel	9 (2.3)	4 (2)	5 (2.5)	1.000
ASA + ticagrelor	10 (2.5)	8 (4)	2 (1)	0.105
Bivalirudin application, n (%)	1 (0.3)	0 (0)	1 (0.5)	1.000
Abciximab application, n (%)	16 (4)	10 (5)	6 (3)	0.307

ASA acetylsalicylic acid, *LMWH* low molecular weight heparin

Primary endpoint: bleeding complications within 30 days following PCI

As shown in **Table 3** bleedings are classified according to BARC, TIMI, and GUSTO as well as FERARI. Due to bleeding events consisting mainly of minor hematomas, BARC type 1 bleeding constituted the majority of bleeding complications. BARC type 4 bleeding was not present in our study cohort because it is directly linked to CABG. For a similar reason, "minimal" in TIMI classification applied for 84% of bleeding events and only "mild" subgroup of GUSTO classification was existent in the StarClose SE® group. The rates of overall and non-access site bleeding were significantly higher in the AngioSeal™ group (p = 0.012; p = 0.003), whereas access site bleedings did not significantly differ between both groups (p > 0.05) **(Table 4)**. The significantly higher rate of non-access site bleeding in the AngioSeal™ group was shown to be related with increased bleeding requiring medical attention in TIMI classification, BARC Type 2 bleeding and mild GUSTO bleedings in this group (p = 0.008; p = 0.0002; p = 0.028). Focusing on FERARI bleedings, a significantly higher rate of complicated bleeding including active bleeding, dissection, fistula, pseudoaneurysm, retroperitoneal hematoma, arterial occlusion, or need of surgical repair was observed in the AngioSeal™ group (p = 0.011).

Secondary endpoint: MACE within 30 days following PCI

In this study MACE occurred rarely and did not differ significantly between both groups **(Table 4)**. None of the two deaths, which occurred within 30 days of follow-up, was related to any bleeding complication. In addition, no significant differences of TVR and TLR were observed in both groups.

Table 3. Comparison of bleedings according to bleeding classification systems in the study

	All (n=400)	StarClose (n=200)	Angio Seal (n=200)	p value*
BARC, n (%)				
Type 1	172 (43.1)	84 (42)	88 (44)	0.686
Type 2	21 (5.3)	2 (1)	19 (9.5)	**0.0002**
Type 3	6 (1.5)	1 (0.5)	5 (2.5)	0.215
Type 4	0 (0)	0 (0)	0 (0)	1.000
Type 5	0 (0)	0 (0)	0 (0)	1.000
TIMI, n (%)				
Minimal	168 (42)	79 (39.5)	89 (44.5)	0.311
Requiring medical attention	30 (7.5)	8 (4)	22 (11)	**0.008**
Minor	1 (0.3)	0 (0)	1 (0.5)	1.000
Major	0 (0)	0 (0)	0 (0)	1.000
GUSTO, n (%)				
Mild	196 (49)	87 (43.5)	109 (54.5)	**0.028**
Moderate	1 (0.3)	0 (0)	1 (0.5)	1.000
Severe or life threatening	2 (0.5)	0 (0)	2 (1)	0.499
FERARI, n (%)				
Small, < 5cm	93 (23.3)	51 (25.5)	42 (21)	0.287
Intermediate, 5-15cm	49 (12.3)	19 (9.5)	30 (15)	0.093
Large, > 15cm	33 (8.3)	15 (7.5)	18 (9)	0.586
Complicated [1]	11 (2.8)	1 (0.5)	10 (5)	**0.011**

* p values for the comparison of femoral closure by StarClose versus femoral closure by AngioSeal group, significant p values are in bold type (p < 0.05)

[1] *Complicated* active bleeding, dissection, fistula, pseudoaneurysm, retroperitoneal hematoma, arterial occlusion or need of surgical repair

Multivariable logistic regression analyses for the primary endpoint

The primary endpoint was adjusted within multivariable logistic regression analyses including the following statistically different variables (**Table 1**

and 2): Preexisting antiplatelet therapy, anticoagulation treatment before PCI with ASA or LMWH, mono loading following PCI with ASA, clopidogrel, prasugrel or ticagrelor, age, sheath size, peripheral vascular disease and renal function.

None of the above described variables were associated with consistent impact on the primary endpoint in multivariate logistic regression models **(Table S1 and S2)**. Notably, neither sheath diameters nor antithrombotic therapies effected any bleeding.

Table 4. Primary and secondary endpoints in the study

	All (n=400)	StarClose (n=200)	AngioSeal (n=200)	p value*
Primary Endpoint				
Overall Bleedings (Access and Non Access Site), n (%)	199 (49.8)	87 (43.5)	112 (56)	**0.012**
Non Access Site Bleedings, n (%)	13 (3.3)	1 (0.5)	12 (6)	**0.003**
Access Site Bleedings, each n (%)				
Hematoma	175 (43.8)	85 (42.5)	90 (45)	0.614
Bleeding	2 (0.5)	0 (0)	2 (1)	0.499
Dissection	3 (0.8)	1 (0.5)	2 (1)	1.000
Fistula	1 (0.3)	0 (0)	1 (0.5)	1.000
Aneurysm	5 (1.3)	0 (0)	5 (2.5)	0.061
Re-hospitalization due to access site bleeding, n (%)	2 (0.5)	0 (0)	2 (1)	0.499
MACE				
Death within follow-up, n (%)	2 (0.5)	1 (0.5)	1 (0.5)	1.000
Myocardial infarction, n (%)	2 (0.5)	0 (0)	2 (1)	0.499
Stent thrombosis, n (%)	2 (0.5)	1 (0.5)	1 (0.5)	1.000
TLR, n (%)	3 (0.8)	2 (1)	1 (0.5)	1.000
TVR, n (%)	2 (0.5)	2 (1)	0 (0)	0.499
Stroke, n (%)	2 (0.5)	0 (0)	2 (1)	0.499

MACE major adverse cardiac events, *TLR* target lesion revascularization, *TVR* target vessel revascularization.

* *p* values for the comparison of femoral closure by StarClose versus femoral closure by AgioSeal group, significant *p* values are in bold type ($p < 0.05$).

Discussion

The present study compared directly two mechanistically different types of FC devices (AngioSeal™ versus StarClose SE®) were focusing on bleedings and MACE in patients undergoing PCI. In case of successful implantation, FC by the extravascular StarClose SE® was significantly associated with lower rates of overall and non-access bleeding as well as complicated access site bleeding compared to the intravascular AngioSeal™. However, the other types of access site bleeding including small, intermediate, or large hematomas did not differ significantly between both groups. None of the above described univariable significant risk factors had consistent impact on the primary endpoint after multivariate adjustment.

Recent studies suggested that both arterial access site and non-access site bleedings following PCI were significantly associated with increased short- as well as long-term mortality regardless of bleedings` origin. [15, 18]. Accordingly, multidisciplinary approaches with improved medical therapy and innovative interventional closure devices as well as techniques have been developed to minimize risk of bleeding and to improve consequently the clinical outcomes [19, 20]. Especially, in the case of access site bleeding, TRA was shown to decrease significantly the rate of procedure related bleedings as well as short- and long-term mortality compared to TFA in many recent prior studies [21-23]. Notwithstanding, TFA is still frequently utilized because of the above mentioned disadvantages of TRA [24], especially in patients with high-risk STEMI and complex PCI [25].

In order to compensate higher risk of bleeding in using TFA compared to TRA, the application of VCDs was already proposed in the early 1990's. [26, 27]. In a clinical trial by Gregory et al. the risk of vascular complications was significantly lower with VCD (AngioSeal™) compared to manual compression both in patients undergoing diagnostic coronary angiography (OR 0.43, 95% CI 0.31 - 0.60) and PCI (OR 0.51, 95% 0.31 - 0.81) [28]. Furthermore, Sanborn et al. demonstrated decreased adverse clinical outcomes in STEMI patients undergoing PCI with application of VCD compared to manual compression (hazard ratio [HR] 0.61, 95% CI 0.42 - 0.89, $p = 0.009$) [29].

However, it is still debatable which kind of VCDs may be the preferred device in terms of efficacy and safety. Schulz-Schupke et al. demonstrated in their randomized study that vascular access site complications were not statistically but numerically lower in patients assigned to the intravascular VCD compared to the extravascular VCD after diagnostic coronary angiography [8]. Additionally, both time to adequate hemostasis and closure device failures were significantly lower in patients with application of the intravascular VCD. These more favorable results of hemostasis with the intravascular compared to the extravascular VCD may be explained by the tighter fixation resulting from more tension of an intravascular VCD. Contrastively, in another study investigated in a diagnostic setting by Veasey et al. the extravascular VCD (StarClose SE®) was significantly associated with less hematoma one week post-procedure compared to the intravascular VCD (AngioSeal™) [30].

Following PCI with concomitant anticoagulation, the application of AngioSeal™ was shown to reduce significantly the rate of TIMI minor (5.5% for AngioSeal™, 6.9% for StarClose SE®, $p < 0.01$), TIMI major (1.2% for AngioSeal™, 2.4% for StarClose SE®, $p < 0.05$), and all bleeding complications (9.2% for AngioSeal™, 10.2% for StarClose SE®, $p < 0.001$) compared to StarClose SE® irrespective of anticoagulation [31]. However, the intravascular VCD was significantly associated with a

higher rate of surgical repair due to distal embolization of either the anchor footplate alone or in combination with thrombus compared to extravascular VCD (0.7% for AngioSeal™, 0.2% for StarClose SE®, $p < 0.05$). Yeni et al., however, found no significant differences of vascular and bleeding complications between intravascular and extravascular devices after PCI [32]. Interestingly, a recent comparison of AngioSeal™ and StarClose SE® in non-cardiological procedures revealed also no statistically significant difference between both groups in terms of bleedings and time to hemostasis [33].

Remarkably, in contrast to other prior studies, the present compared directly two mechanistically different VCDs after PCI and revealed that the intravascular AngioSeal™ was associated with significantly rate of overall, non-access as well as complicated access site bleeding compared to extravascular StarClose SE®.

Despite the use of both VCDs the rates of access site bleeding appeared to be higher than expected in the FERARI study. Access site bleedings were shown in about 43% of patients in the StarClose SE® group and 50% of patients in the AngioSeal™ group. The higher rate of procedure related bleedings might be explained by the more detailed discrimination of minor bleedings within FERARI classification. In contrast to other bleeding classifications the FERARI classification reflect more precisely most common types of exercised bleeding and hematomas smaller than 5cm (23.3%). These small hematomas contributed to low-graded bleedings within the other classification systems, i.e. BARC type 1, TIMI minimal, and GUSTO mild.

Many previous studies assessed a significant association of major bleedings following PCI with major adverse outcomes [34, 35]. However, in the present study the difference of bleeding rates in both treatment groups did not affect the development of MACE. Furthermore, no significant differences of TLR or TVR rates were observed in between AngioSeal™ and StarClose SE® group.

Conclusions

In case of successful implantation, FC by the AngioSeal™ is associated with higher rates of both access and non-access site bleedings. However, no significant difference of MACE at 30 days was observed in the AngioSeal™ and StarClose SE® group. The FERARI classification was shown to better discriminate access site complications following PCI.

Supplementary Material

Supplementary tables.
http://www.medsci.org/v16p0043s1.pdf

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Competing Interests

The authors have declared that no competing interest exists.

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