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Controversies in Cardiology

Simplified swift and safe vascular closure device deployment without a local arteriogram: Single center experience in 2074 consecutive patients☆

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ABSTRACT

Objective: Vascular closure devices (VCDs), such as the Angio-Seal, a three-component hemostatic plug, have greatly facilitated the routine clinical practice in the catheterization laboratory. The manufacturer recommends a local angiogram before Angio-Seal deployment. However, from the outset, we employed a simplified routine of deploying this VCD, i.e. without use of local angiography.

Methods: The Angio-Seal was employed without a preceding femoral arteriogram over 8 years in 2074 consecutive patients, 72% presenting with acute coronary syndromes and subjected to coronary angiography ($n = 1032$) or PCI $n = 1042$) via a transfemoral approach with use of heparin and dual antiplatelet therapy.

Results: Deployment of the VCD was successful in 99.4%. Complete hemostasis was obtained in 98% of cases. In 14 patients, Angio-Seal deployment failed. Mean time for placement of Angio-Seal was <1 min, to-hemostasis 1 min, and to-mobilization 3 h. Only 3 (0.15%) patients had a major complication with vessel occlusion that required emergent vascular surgery with a successful outcome. Two patients developed a local pseudoaneurysm treated with ultrasonography-guided compression. Six small and 4 large inguinal hematomas (one requiring blood transfusion) and 5 cases of retroperitoneal bleeding (one requiring blood transfusion) were recorded.

Conclusion: Deployment of Angio-Seal without use of local angiography was efficacious and safe, characterized by a high success rate of deployment and hemostasis with few correctable complications in a large patient cohort undergoing transfemoral catheterization for PCI and non-PCI procedures under anticoagulation and antiplatelet drug therapy. VCD reduced the time-to-hemostasis and time-to-mobilization and minimized the incidence of complications.

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Abbreviations: ACS, acute coronary syndrome(s); DM, diabetes mellitus; PCI, percutaneous coronary intervention; VCD, vascular closure device.

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1. Introduction

Vascular closure devices (VCDs) have an increasingly important role in the catheterization laboratory during coronary angiography and percutaneous coronary interventions (PCI), as an alternative to manual or mechanical compression.[1–3] Of course, nowadays, VCDs have a great competitor of growing importance, i.e. the radial access.[4] Nevertheless, their use offers expedience, safety, patient convenience and early ambulation, and reduced hospital resources and costs. Ample experience has been obtained in our laboratory with routine use of such a device, Angio-Seal™ (St. Jude Medical, St. Paul, MN, USA), for femoral artery puncture site closure and hemostasis. Angio-Seal consists of three resorbable components, a polymer anchor, the collagen plug, and a suture, which are introduced with the aid of a delivery system and seal the arterial puncture site. The manufacturer recommends that before considering Angio-Seal use, a femoral angiogram of the site is indicated. However, a local angiogram increases the amount of radiation exposure, particularly important for the groin area exposure in younger patients, as well as the load of intravascularly administered contrast with its attendant consequences, especially in older diabetic patients or patients with renal insufficiency. From the outset, we employed a simplified routine for the deployment of the VCD, i.e. without use of local angiography and herein report the results of this approach in a large cohort of patients undergoing transfemoral catheterization.

2. Patients and methods

2.1. Patients

Over the last 8 years, the Angio-Seal VCD was employed in 2074 consecutive patients who were submitted to catheterization by our team of 3 operators via a transfemoral approach in order to perform coronary angiography, renal percutaneous angioplasty, aortography, or PCI. Patients ($n = 90$) were excluded when transfemoral access was considered problematic or impossible due to peripheral vascular disease, requiring a transradial approach or deemed as best suited for manual compression rather than use of a VCD; also patients catheterized during periods when the VCD was not available for use in our catheterization laboratory due to a limited supply from the manufacturer were not included in this series. Possible complications and risks, as well the benefits of each procedure were all made explicit to the patient and the patient's family, and informed written consent was obtained from the patient before the procedure.

2.2. Vascular access

Vascular access was routinely obtained via puncture of the right femoral artery and occasionally via the left femoral artery in cases where vascular access problem was anticipated or encountered from the right femoral artery or when repeat access was required within a short period after puncture of the right femoral artery.

Selection of the entry site was guided most commonly by a combination of external anatomical landmarks. Usually, the artery was entered 2–3 cm below the midpoint of the inguinal skin crease or at the midpoint between the anterior superior iliac spine and pubic tubercle, guided by palpation of the maximal arterial pulse. One operator mostly used the fluoroscopy-guided technique using visualization of the femoral head in a posterior-anterior projection with the skin puncture done at a point between the lower border and the mid portion of the head of femur.

After adequate local anesthesia with subcutaneous xylocaine, arterial access was obtained with use of an 18-gauge needle and a modified Seldinger technique with an attempt to limit the stick to the anterior arterial wall and avoid posterior wall puncture. A 6 French femoral sheath was routinely used except when a demanding PCI procedure was planned, in which case a 7 French sheath was employed. After arterial access was secured, 2500 U of intravenous unfractionated heparin was given.

2.3. Percutaneous coronary intervention

All patients submitted to PCI received a bolus of 7000 units of heparin after obtaining vascular access for elective procedures or right after completion of coronary angiography for ad hoc PCI procedures. Additional heparin (2000 units/h) was administered for procedures lasting longer than 1 h if the activated clotting time (ACT) could not be monitored or if ACT was measured, heparin was given in doses needed to maintain the ACT >300 s throughout the procedure. A variety of coronary stents were implanted, including bare metal stents, endothelial progenitor cell capture stents, micro net mesh covered stents, and drug-eluting stents.

For pre-planned procedures an attempt was made to use pretreatment with at least a pre-procedural 3-day regimen of aspirin (325 mg daily) and clopidogrel (75 mg daily); for patients not having been on aspirin or clopidogrel before the procedure, a loading dose of 500 mg and 300–600 mg of each medication, respectively, was given the day of the procedure. For patients with angiographically demonstrated intracoronary thrombi, particularly those with acute ST-elevation myocardial infarction, or other high-risk patients, e.g. diabetic patients receiving multiple stents, glycoprotein IIb/IIIa inhibitors were used, including eptifibatide or tirofiban.

2.4. Vascular closure device

When the procedure was completed, reversal of the effect of heparin was not performed. A guidewire was introduced via the sheath into the artery and then the sheath was removed immediately without checking the ACT, while maintaining pressure above the access site to ensure continued hemostasis. Subsequently, the VCD was deployed over the guidewire.

The Angio-Seal vascular closure device delivery system comprises the Angio-Seal device, an insertion sheath, an arteriotomy locator, and a guidewire. The Angio-Seal device is composed of an absorbable collagen sponge and a specially designed absorbable polymer anchor that are connected by an absorbable self-tightening suture (Fig. 1). The device seals and interposes the arteriotomy between the anchor located

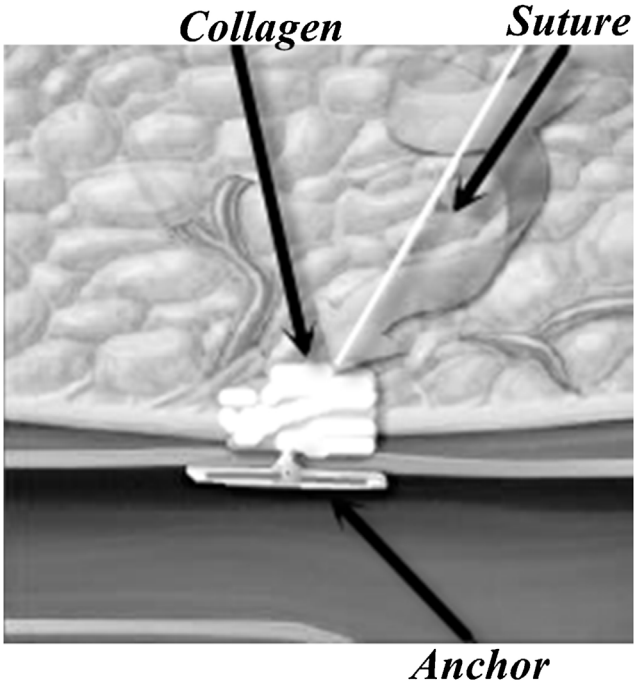

Fig. 1 – Angio-Seal has three resorbable components, a polymer anchor, the collagen plug, and a suture, which are introduced with the aid of a delivery system and seal the arterial puncture site. The resorbable polymer anchor and suture are placed within the artery and pulled back to the entry site to secure the placement of the collagen plug just outside the arterial wall.

intravascularly and the collagen plug located extravascularly. Hemostasis is achieved primarily by the mechanical means of the anchor – arteriotomy – collagen infix, which is supplemented by the coagulation-promoting properties of the collagen. The device is contained in a delivery system that stores and then delivers the absorbable components to the arterial puncture. The 8-French Angio-Seal device was employed for 8- or 7-French procedural sheaths and the 6-French Angio-Seal device was used for a 6 French or smaller procedural sheath. Three types (generations) of the Angio-Seal VCD were employed during the study period (Angio-Seal, Angio-Seal VIP, and Angio-Seal STS plus).

2.5. *Deployment technique*

Utilizing a new pair of sterile gloves and after cleansing the groin around the sheath with betadine, the packet with the Angioseal device was opened. First, the arteriotomy locator was inserted into the Angio-Seal sheath aligned and snapped in place. Then, this assembly was inserted over the guidewire and advanced into the artery until blood squirting from the drip hole on the locator was noted. Then, holding the insertion sheath steady, the arteriotomy locator and guidewire were removed. Holding the hub of the sheath in position with the left hand, the Angioseal device was then advanced into the sheath with the reference indicator on the device and the hub of the sheath on the same side facing each other. After snapping the Angioseal device in position, the hub of the sheath was held with one hand and the cap of the device was pulled away from the hub until resistance was felt, indicating that the anchor was at the distal tip of the sheath. The device sheath assembly was pulled in the direction of the track to allow the anchor to get positioned against the vessel wall. Pulling was then continued and tension maintained on the device sheath assembly to expose the tamper, which was then advanced into the track to compact the collagen. Once hemostasis was achieved and resistance was felt, advancing the tamper was stopped, the suture was cut below the clear stop and the tamper tube was removed. The exposed loose suture was further cut below the skin line by holding tension on the thread. A sterile dressing was placed afterwards at the entry site and pressure was applied for ~2 min. All 3 operators employed the same uniform technique of VCD deployment with a short and smooth learning curve.

An attempt was made to record the time to hemostasis and to ambulation after the deployment of the VCD. Complications were recorded in every patient when they occurred. All data were collected prospectively. All patients were followed closely until discharge.

2.6. *Recording of complications*

The occurrence of a pseudoaneurysm, arterio-venous fistula, arterial thrombosis, need for vascular surgery, retroperitoneal bleed, local abscess, bleeding or large (>10 cm) hematoma at the puncture site requiring transfusion, or in-hospital death attributed to VCD complication were considered as major complications. Routine duplex ultrasound was not performed to check the puncture site unless there was a clinical suspicion of a pseudoaneurysm or a fistula. A minor complication was defined as a localized allergic reaction or cellulitis or a hematoma not requiring transfusion. Failure to anchor the device and/or deliver the collagen to the puncture site was recorded as VCD deployment failure.

2.7. *Statistical analysis*

The data are summarized as mean ± standard deviation or median (interquartile range) for continuous variables, and count and/or proportions for categorical variables. Differences in baseline parameters or exposure variables were determined by 2-tailed Student's *t*-test or analysis of variance for quantitative data and by chi-square statistic or Fischer's exact test, when appropriate, for qualitative data. Data with no normal distribution were compared with Mann–Whitney test. The association of baseline exposure variables with major endpoints was assessed through binary logistic regression. Univariate logistic regression models were initially implemented and subsequently significant predictors were included in the final multivariable analysis. Parameters incorporated in the final analysis included the access site, age, gender, diabetes, hypertension, hypercholesterolemia, smoking status, use of IIb/IIIa agents, type (generation) of VCD, and type of procedure (PCI vs non-PCI). Finally, a bootstrap resampling procedure[5] was used to confirm optimal model selection. Model calibration was assessed by comparing predicted probabilities with observed probabilities. Goodness of fit was

estimated by the Hosmer–Lemeshow test. Receiver Operating Characteristic (ROC) curves analysis was used in order to assess whether exposure variables could incrementally identify increased risk for major complications. The curves were constructed by plotting sensitivity against (1-specifity) and corresponding Area(s) Under the Curve (AUC) were compared.

Statistical analysis was performed with STATA package, version 11.1 (StataCorp, College Station, Texas, USA). Statistical significance was set at $p < 0.05$. In terms of power considerations, the baseline probability for incidence of the primary endpoint was set as low as 1% and Type I error was predefined at 0.05. The recruited sample size provided 80% power to detect a significant change of 50% in odds of the primary endpoint occurrence (from 1% to 1.5%) for one unit increase in the corresponding exposure variable. Power calculations were performed with G*Power, version 3.0.10.

3. Results

3.1. Procedural characteristics

Clinical and procedural characteristics of the study population are described in Table 1. Of a total of 2164 patients catheterized in our laboratory during the study period, 2074 patients received a VCD and were included in the study. These were 1563 (75.4%) men and 511 women, aged 64.6 ± 12.2 years (range, 18–93). The VCD was used in two groups of patients, 1042 patients undergoing a PCI procedure and 1032 having a non-PCI procedure (mostly coronary angiography or occasionally renal angiography and/or renal artery angioplasty). Male gender, smoking status, dyslipidemia, and impaired ejection fraction were significantly greater in the subgroup of subjects allocated in the PCI group (Table 1).

History of diabetes mellitus (DM) was present in 606 (29.2%) patients, of hyperlipidemia in 1436 (69.2%) patients, of hypertension in 1317 (63.5%), while 772 (37.2%) patients were current smokers. The majority (72%) were patients admitted with an acute coronary syndrome (ACS). A total of 1042 (50.2%) patients underwent a PCI procedure, which was performed ad hoc (during the same session as coronary angiography) in 983 (94.3%) patients. PCI was performed on a mean number of vessels of 1.3 ± 0.6 with a mean of 2.4 ± 1.4 lesions dilated and/or stented. Stents were used in 1017 (97.6%) patients, bare metal stents in 23 (3%) patients, endothelial progenitor cell capture stents in 211 (21%) patients, and drug-eluting stents in 775 (76%) patients. The mean left ventricular ejection fraction was 49.2 ± 11.6% (range, 15–75%). A platelet glycoprotein IIb/IIIa inhibitor was administered in 297 (14.3%) patients.

The right femoral artery was accessed in 1979 patients, the left femoral artery in 90 patients, and both femoral arteries in 5 patients. The first generation of the VCD (Angio-Seal) was employed in the first 244 patients, the second generation device (Angio-Seal VIP) in 63 patients, and the latest generation device (Angio-Seal STS plus) in the subsequent 1767 patients. Successful VCD deployment was achieved in 2060 (99.3%) patients. In 14 patients (7 in each group), insertion of the device failed partially or completely, and in all these cases, manual compression was applied. The mean time required for the placement of Angio-Seal was <1 min. The mean time-to-hemostasis was also <1 min. The mean time-to-mobilization was 3 h.

3.2. Complications

Acute occlusion of the femoral artery occurred in 3 (0.14%) patients who required vascular surgery, which successfully restored patency of the femoral artery by removing either thrombotic material ($n = 2$) or the occluding anchor of the

Table 1 – Characteristics of 2074 consecutive patients submitted to PCI or non-PCI procedures, who received a vascular closure device.

	All patients	PCI	Non-PCI	*p* value
Patients	2074	1042	1032	
Men/Women	1563/511	840/202	723/309	<0.001
Age (years), mean ± SD	64.6 ± 12.2	64.3 ± 12.3	64.9 ± 12.2	0.210
Clinical presentation				
Acute coronary syndrome, *n* (%)	1.497 (71.9%)	902 (86.6%)	595 (57.7%)	<0.001
Risk factors				
Smoking, *n* (%)	772 (37.2%)	459 (44%)	313 (30.3%)	<0.001
Hypertension, *n* (%)	1317 (63.5%)	642 (61.6%)	675 (65.4%)	0.727
Dyslipidemia, *n* (%)	1436 (69.2%)	779 (74.8%)	657 (63.7%)	<0.001
DM, *n* (%)	606 (29.2%)	290 (27.8%)	316 (30.6%)	0.163
LVEF (%)	50 (40–60)	55 (40–60)	50 (40–55)	0.013
Access site				
RFA, *n* (%)	1979 (95.4%)	988 (95.7%)	991 (95.2%)	
LFA, *n* (%)	90 (4.3%)	41 (4%)	49 (4.7%)	
RFA + LFA, *n* (%)	5 (0.2%)	3 (0.3%)	2 (0.2%)	0.648
Adjuvant therapy				
IIb/IIIa agents, *n* (%)		297 (28.5%)		NA

DM, diabetes mellitus; LFA, left femoral artery; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; RFA, right femoral artery; NA, not applicable.

Table 2 – Outcome and complications in the PCI and non-PCI Groups.

Parameters	All patients (*n* = 2074)	PCI group (*n* = 1042)	Non-PCI group (*n* = 1032)	*p* value
Outcomes				
Successful deployment, *n* (%)	2060 (99.4%)	99.4%	99.4%	0.999
Failed deployment, *n* (%)	14 (0.6%)	7 (0.6%)	7 (0.6%)	0.999
Complications				
Need for local surgery, *n* (%)	3 (0.15%)	2 (0.19%)	1 (0.1%)	0.569
Retroperitoneal bleeding, *n* (%)	5 (0.24%)	4 (0.38%)	1 (0.1%)	0.183
Groin bleeding/hematoma, *n* (%)	10 (0.48%)	8 (0.77%)	2 (0.2%)	0.028**
Pseudoaneurysm, *n* (%)	2 (0.1%)	1 (0.1%)	1 (0.1%)	0.999
AV fistula, *n* (%)	0			NA
Local infection, *n* (%)	0			NA
Vagotonia, *n* (%)	5	4	1	0.183
Rigors/Allergy, *n* (%)	3	3	0	0.085**
Overall complications, *n* (%)	28 (1.35%)	22 (2.11%)	6 (0.01%)	0.001
*In-hospital mortality, *n* (%)	5 (0.24%)	4 (0.38%)	1 (0.1%)	0.18

AV, arteriovenous; NA, non-applicable; PCI, percutaneous coronary intervention.
* Unrelated to VCD (see text for discussion).
** Continuity correction performed.

device (*n* = 1). No patient had an arterio-venous fistula. Two patients developed a pseudoaneurysm of the right common femoral artery; the lesion was treated with ultrasonography-guided compression. In addition, 6 small/moderate local hematomas and 4 large inguinal hematomas were recorded (Table 2); one patient with a large hematoma required blood transfusion. In 5 cases (4 in the PCI and 1 in the non-PCI group), retroperitoneal bleeding occurred, requiring blood transfusion in one of them; 3 patients were receiving a IIb/IIIa inhibitor. No cases of local infection were observed. Overall, complications were higher ($p < 0.001$) in the PCI group but significant difference in individual categories was established only for groin hematoma.

3.3. *Risk predictors*

Female gender, procedure type (PCI), generation of VCD, DM type II (marginal), and administration of IIb/IIIa were significant predictors in univariate analysis for complications after VCD use (Table 3). Multivariate analysis indicated that female gender (odds ratio – OR = 3.99, 95% confidence intervals – CIs: 2.01–7.98; $p < 0.0001$), use of a IIb/IIIa agent (OR = 2.87, 95% CIs: 1.24–6.62; $p = 0.014$), DM (OR = 0.354, 95% CIs: 0.145–0.866; $p = 0.023$), and the generation of VCD (OR = 0.361, 95% CIs: 0.168–0.776; $p = 0.009$) independently predicted the major endpoint of the study. Access through the left femoral artery (LFA) or both femoral arteries was marginally associated with higher risk (OR = 2.45, 95 CIs: 0.878–6.81). Conversely, age, traditional risk factors, and procedure type (PCI versus catheterization) did not confer a higher risk. The protective role of DM was not mediated by the exposure variables included into the multivariable model as indicated by the lack of statistical significance of all interaction terms that were tested (exposure variables in Table 3 *DMII, $p > 0.05$ for all). In a subgroup of patients with data for left ventricular ejection fraction (LVEF) available (*n* = 644), a multivariable model identical to Table 3 plus LVEF at baseline (OR = 0.987, 95% CIs: 0.94–1.04, $p = 0.611$) indicated a non-significant association of DMII (OR = 0.408, 95% CIs: 0.08–2.15; $p = 0.291$) with risk of

Table 3 – Association of baseline exposure variables with the incidence of major complications in our study through logistic regression analysis.

Variables	Univariate		Multivariable	
	Odds ratio (95% CIs)	*p*-value	Odds ratio (95% CIs)	*p*-value
Age	1.023 (0.995–1.052)	0.103	1.019 (0.989–1.05)	0.25
Gender (Female)	3.31 (1.75–6.25)	<0.001	3.99 (2.01–7.98)	<0.001
Smoking (yes)	0.746 (0.376–1.48)	0.402	0.852 (0.381–1.9)	0.696
Hypertension (yes)	1.3 (0.654–2.58)	0.454	1.18 (0.571–2.46)	0.649
DM (yes)	0.435 (0.182–1.04)	0.062	0.354 (0.145–0.866)	0.023
Dyslipidemia (yes)	1.29 (0.627–2.67)	0.485	1.03 (0.485–2.19)	0.938
Type of procedure (PCI)	2.26 (1.14–4.49)	0.02	1.8 (0.81–3.98)	0.149
IIb/IIIa agent administration (yes)	3.058 (1.55–6.02)	0.001	2.87 (1.24–6.62)	0.014
Access site (LFA/both)	1.76 (0.532–5.81)	0.354	2.45 (0.878–6.81)	0.087
Type of VCD(PLUS)	0.694 (0.15–3.22)	0.641	0.448 (0.9–2.26)	0.326
(VIP)	0.316 (0.154–0.649)	0.002	0.361 (0.168–0.776)	0.009

CI, confidence intervals; DM, diabetes mellitus; LFA, left femoral artery; PCI, percutaneous coronary intervention; VCD, vascular closure device. Odds ratios are provided for the category of interest denoted in parentheses below the column "Variables".

complications, while retaining the remaining significant predictors (female gender, IIb/IIIa use and type of VCD, $p < 0.05$) and might suggest a residual unadjusted confounder.

When additional adjustment for peripheral artery disease (OR = 2.39, 95 CIs: 0.56–10.22; $p = 0.240$) was performed, independent predictors for higher risk of complications retained their statistical significance (gender, DM, IIb/IIIa and generation of VCD, $p < 0.05$ for all three). Relevant results were established when alternative confounders, not indicated by univariate analysis or the bootstrap technique, were

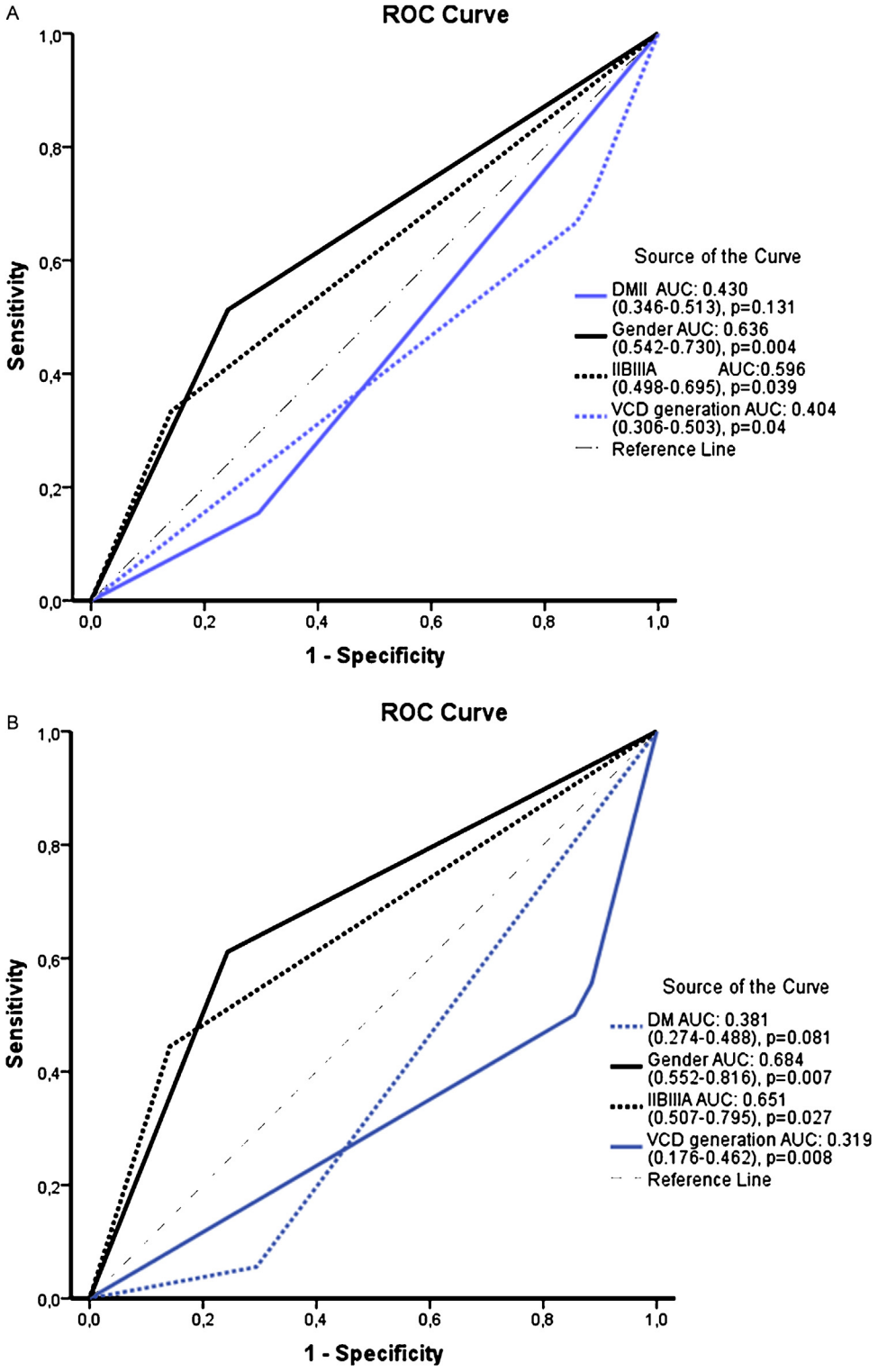

Fig. 2 – Receiver operator curves (ROC) for main predictors of: (A) total complications; (B) major complications in our study. Area Under the Curve (AUC) for each parameter of interest is provided in median value (95% confidence intervals). P-values <0.05 denote significant difference of AUC from 0.5 (under the null hypothesis the true AUC is 0.5 for classification variables).

incorporated in the final multivariable model: adjustment for urgent/emergent versus elective catheterization, number of lesions/vessels dilated and/or stented neither impoverished the aforementioned associations with gender, IIb/IIIa use, VCD generation and DM ($p < 0.05$ for all) nor established new predictors ($p > 0.05$ for all). When the endpoint of complications was limited for major adverse events only, relevant logistic regression analysis did not substantially alter our results. Female gender (OR = 9.28, 95 CIs: 3.13–27.5; $p < 0.001$), IIb/IIIa administration (OR = 3.43, 95 CIs: 1.022–11.5; $p = 0.046$), and VCD generation (OR = 0.204, 95 CIs: 0.072–0.58; $p = 0.003$) were the only independent predictors of complications after VCD use. DMII remained a marginal protective predictor (OR = 0.135, 95 CIs: 0.017–1.05; $p = 0.056$) for major complications. All the additional adjustments (urgent/emergent versus elective catheterization, number of lesions/vessels) did not change the main associations described above. As with extended complications, adjustment for LVEF in 644 subjects rendered the association of DMII with decreased risk not significant (OR = 0.658, 95 CIs: 0.058–7.45; $p = 0.736$).

Among exposure variables, female gender increased most the odds of presenting a complication with VCD use. After adjusting for all major confounders, female subjects had a 4-fold increase in all adverse events and a 9-fold increase in major complications in comparison to male subjects. Table 2 summarizes non-parametric ROC analysis in terms of AUC that correspond to each baseline predictor. In both endpoints, gender was associated with significantly increased AUC but relative differences with AUC corresponding to other predictors were not established (Fig. 2). An incremental predictive role was not established for none of female gender, VCD generation, DM, and IIb/IIIa use when AUCs for nested multivariable models were compared (e.g. AUC of multivariable model without gender versus AUC of full model, $p > 0.05$ for all comparisons).

3.4. *In-hospital mortality*

During hospitalization, 5 patients, 4 (0.38%) in the PCI and 1 (0.1%) in the non-PCI group, succumbed to their disease. There was no apparent relation to use of the VCD. No local vascular complication was noted in any of the 4 PCI patients. One death occurred suddenly 8 h after successful PCI of the left circumflex; one death occurred in an elderly patient 3 days after PCI of a saphenous vein graft complicated by no-reflow; one heart failure death occurred in a nonagenarian patient 2 days after successful PCI of two vessels; one patient sustained a new fatal anterior myocardial infarction 3 days after a complicated PCI of a saphenous vein graft to the left circumflex; finally, a heart failure death occurred in one elderly patient with mitral stenosis, non-significant coronary artery disease and compromised left ventricular function 2 weeks after coronary angiography; this patient developed retroperitoneal hematoma post-procedurally; however, she did not require any blood transfusion.

4. Discussion

The present study demonstrates in a series of 2074 consecutive patients of three operators' experience that the AngioSeal was a very effective VCD, with a 99.3% successful deployment rate, in a swift and simple procedure obviating the need for performance of local angiography to guide deployment. A local angiogram increases both the duration of radiation exposure, particularly important for the groin area exposure in younger patients, as well as the load of intravascularly administered contrast with its attendant risks, especially in older diabetic patients or patients with renal insufficiency, which can all be potentially avoided with use of our suggested approach. These results are, of course, commensurate with the ability to perform an arterial puncture at the appropriate site, which is considered to be the common femoral artery.[1] Thus, avoiding low femoral arterial entry or puncture above the inguinal ligament was apparently of critical importance. This was achieved by use of external and/or fluoroscopic landmarks and a modified Seldinger's technique, but without use of femoral angiography.

The mechanical seal achieved with Angio-Seal (Fig. 1) produces virtually immediate hemostasis, allowing the procedure to be completed in the catheterization laboratory. The three components of this VCD, suture, collagen, and anchor, used to seal the puncture site, are fully resorbable within 60–90 days. Immediate repeat puncture of the artery, if and when needed, is safe to perform without an increased risk of vascular complications.

The reasoning behind the instruction of the manufacturer to use a local angiogram to guide VCD deployment relates to avoidance of complications (http://www.pei.ie/PEI/media/PEI-media/PDFs/PDFs_Cardiac/PDFs_Cardiac_Products/angio-seal_evolution_ifu_us.pdf). Thus, the recommendation is not to use the Angio-Seal device if the procedure sheath has been placed through the superficial femoral artery and into the profunda femoris as this may result in collagen being placed into the superficial femoral artery, leading to arterial thrombosis and symptoms of acute distal ischemia. In the same line, the Angio-Seal device should not be used if the puncture site is at or distal to the bifurcation of the superficial femoral and profunda femoris artery, as this may result in the anchor entrapped in the bifurcation or being positioned incorrectly, and/or collagen deposition into the vessel, all potentially leading to vessel occlusion. Lastly, the Angio-Seal device should not be used if the puncture site is proximal to the inguinal ligament as this may result in retroperitoneal bleeding.

All these important issues were taken into consideration in the present study and the operators made a conscious attempt to puncture the artery at the optimal site, i.e. above the bifurcation and below the inguinal ligament, albeit without the use of local angiography, in order to avoid all these pitfalls. In addition, an attempt was made to limit the arterial puncture to the anterior wall of the artery and thus avoid deep tissue and/or retroperitoneal bleeding. The technique employed apparently rendered this feasible as inferred by the results of the present study, whereby the complication rate was kept to a minimum with 3 (0.15%) patients suffering from vessel occlusion requiring surgery.

Historically, femoral arterial access for various catheterization procedures has necessitated prolonged (≥20–30 min) manual or mechanical compression and extended (≥6–12 h) bed rest following sheath removal.[1,6,7] Progressively, however,

over the last 1–2 decades, vascular closure devices (VCDs) have ushered in a new era in clinical practice allowing for faster hemostasis at the puncture site, and early ambulation and shorter hospital stay for patients undergoing transfemoral interventional procedures.[1,3,8] VCDs are characterized mainly by the mechanism of hemostasis they provide, which includes biodegradable collagen or other plug, staples, or sutures.[9] However, despite the apparent advantages of VCDs, complications at the site of femoral artery access still occur.[10,11] Newer generation devices appear more promising with improved safety profile.[12] This was also the case in the present study where the newer generation VCD performed better compared to older VCD types. However, due to reports of early failure of even more recent versions of VCD,[13,14] our group avoided the use of this particular model. The need for more efficacious hemostasis is greater for patients undergoing PCI procedures, whereby heavy antithrombotic and anticoagulant therapy has been employed. During such demanding procedures, reversal of the coagulant effect is usually avoided due to risk of coronary vessel occlusion and/or stent thrombosis, and sheath removal is deferred, occasionally for several hours,[8] for the anticoagulant effect to dissipate (e.g. until the measured ACT drops below 180–200 s) and thus reduce the risk of bleeding before manual compression can be successfully applied on the puncture site.

Several trials have examined the efficacy and safety of VCDs,[1,10,15] but there is still lack of strong data from randomized clinical trials establishing the superiority of VCDs over manual or mechanical compression.[16] For both diagnostic and PCI procedures, VCDs are effective and more practical over manual compression, offering more rapid hemostasis and earlier ambulation over manual compression, successfully competing with the transradial approach. Among the potential shortcomings of VCDs, deployment failure is a major issue,[17] but more important are the local vascular complications that may ensue, which may lead to leg ischemia and/or need for vascular surgery with its attendant risks.[18] Data from earlier meta-analyses have cast doubts whether vascular complications were any different between mechanical compression and VCDs; they even suggested some potential harm.[2,10,19] The argument that has been put forth relates to inclusion in these analyses of data from use of earlier generation of VCDs, which have been subsequently withdrawn from the market. When such data are excluded from the analysis, the results become neutral. Furthermore, additional meta-analysis[19] has indicated a significant 11% reduction in vascular complications from 16 PCI studies comprising 5048 patients. More recently, an analysis of the ACUITY trial examining the impact of VCDs and antithrombotic therapy on local bleeding complications showed a significant decrease in major local bleeding associated with VCD use.[20] Similar findings were obtained from a Northern New England PCI registry comprising more than 45,000 patients,[21] and an analysis of the National Cardiovascular Data Registry database comprising more than 1.5 million patients,[22] which showed that both bleeding-avoidance strategies of VCD and bivalirudin use resulted in significant reductions in local bleeding complications. Patients at higher-risk for bleeding had the greatest benefit from use of VCDs. These results compare favorably with reported rates of bleeding via the transradial approach.[4,23]

It appears that VCD use may finally be operator-dependent despite that the learning curve appears to be relatively short. Integration of clinical data, having performed the arterial puncture at the correct site and familiarizing oneself with a particular VCD, seems to play a key role in successfully deploying the device and achieving complete hemostasis and avoiding disastrous local complications.[24] Deployment of older generation VCDs was cumbersome and benefits were not that apparent compared with manual compression, particularly with regard to safety.[2,15,25,26] However, newer generation devices have overcome such limitations and have contributed to reduced local complication rate.[16,27]

In the present study, we have demonstrated a high (99.4%) success rate of initial deployment of the VCD with also a high (98%) rate of successful final hemostasis in a large population of high-risk patients with the majority presenting with acute coronary syndromes undergoing PCI procedures via a transfemoral approach. Use of anticoagulation and/or strong antiplatelet therapy with IIb/IIIa inhibitors on top of dual antiplatelet therapy led, as it might have been expected, to higher, albeit not inordinate, local complication rate. In contrast, only 2 patients sustained major bleeding (inguinal or retroperitoneal) requiring blood transfusion, and only two additional patients developed a local pseudoaneurysm treated conservatively with ultrasound-guided compression.

4.1. *Predictors of local complications*

According to the results of the multivariable analysis in our population, female gender, the presence of diabetes, use of a IIb/IIIa agent, and generation of VCD predicted major and total complications. Conversely, age, and traditional risk factors did not confer a higher risk. A higher complication rate with use of VCDs in women has been previously reported and ascribed to smaller arterial luminal diameters in women.[28]

4.2. *Study limitations*

Although this is a prospective study, it lacks randomization with a control group of patients having manual compression during the same time period. This is because a VCD was employed systematically in all consecutive patients undergoing a catheterization procedure during the study period, except for brief periods when the device was not available or when there were patients having peripheral vascular disease who had the procedure done via a radial or brachial approach, and thus there was no comparable group having concurrent manual compression. The lack of 30-day follow-up in this patient population may be considered as another limitation of the present study, but it has been demonstrated by other studies that most of the adverse events (95.5%) occur during hospitalization.[16]

5. Conclusion

As a bleeding avoidance strategy, Angio-Seal was an efficacious and safe VCD characterized by a high (99.4%) success rate

of deployment without use of local angiography and highly successful hemostasis (98%), with few (1.4%) correctable complications in a very large patient population undergoing transfemoral catheterization for PCI and non-PCI procedures under anticoagulation and antiplatelet drug therapy. In these patients, VCD reduced the time-to-hemostasis and time-to-mobilization and minimized complications. Further randomized studies[16] are needed to more definitively determine efficacy and safety, and examine issues of cost-effectiveness[8] of the transfemoral approach over manual or mechanical compression. More importantly, studies, such as the announced ARISE trial,[29] are needed to compare the transfemoral access routinely using a VCD with the radial approach in terms of speed, effectiveness, safety, and cost-efficacy.[30]

Conflicts of interest

The authors have none to declare.

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REFERENCES

1. Bangalore S, Bhatt DL. Femoral arterial access and closure. *Circulation*. 2011;124:e147–e156.
2. Koreny M, Riedmuller E, Nikfardjam M, Siostrzonek P, Mullner M. Arterial puncture closing devices compared with standard manual compression after cardiac catheterization: systematic review and meta-analysis. *JAMA*. 2004;291:350–357.
3. Dauerman HL, Applegate RJ, Cohen DJ. Vascular closure devices: the second decade. *J Am Coll Cardiol*. 2007;50:1617–1626.
4. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet*. 2011;377:1409–1420.
5. Goliasch G, Kleber ME, Richter B, et al. Routinely available biomarkers improve prediction of long-term mortality in stable coronary artery disease: the Vienna and Ludwigshafen Coronary Artery Disease (VILCAD) risk score. *Eur Heart J*. 2012;33:2282–2289.
6. Manolis AS. Reduced incidence of clinical restenosis with newer generation stents, stent oversizing, and high-pressure deployment: single-operator experience. *Clin Cardiol*. 2001;24:119–126.
7. Mohammady M, Heidari K, Akbari Sari A, Zolfaghari M, Janani L. Early ambulation after diagnostic transfemoral catheterisation: a systematic review and meta-analysis. *Int J Nurs Stud*. 2014;51:39–50.
8. Kerre S, Kustermans L, Vandendriessche T, et al. Cost-effectiveness of contemporary vascular closure devices for the prevention of vascular complications after percutaneous coronary interventions in an all-comers PCI population. *EuroIntervention*. 2014;10:191–197.
9. Lasic Z, Nikolsky E, Kesanakurthy S, Dangas G. Vascular closure devices: a review of their use after invasive procedures. *Am J Cardiovasc Drugs*. 2005;5:185–200.
10. Nikolsky E, Mehran R, Halkin A, et al. Vascular complications associated with arteriotomy closure devices in patients undergoing percutaneous coronary procedures: a meta-analysis. *J Am Coll Cardiol*. 2004;44:1200–1209.
11. Dangas G, Mehran R, Kokolis S, et al. Vascular complications after percutaneous coronary interventions following hemostasis with manual compression versus arteriotomy closure devices. *J Am Coll Cardiol*. 2001;38:638–641.
12. Tavris DR, Wang Y, Jacobs S, et al. Bleeding and vascular complications at the femoral access site following percutaneous coronary intervention (PCI): an evaluation of hemostasis strategies. *J Invasive Cardiol*. 2012;24:328–334.
13. Lupi A, Lazzero M, Plebani L, Sansa M, Bongo AS. Safety and efficacy of the new Angio-Seal Evolution closure device: a single-center experience. *J Invasive Cardiol*. 2011;23:150–155.
14. Lupi A, Rognoni A, Secco GG, et al. Comparison of the novel Angio-Seal Evolution with Angio-Seal STS closure device. *Perspect Vasc Surg Endovasc Ther*. 2012;24:28–36.
15. Shammas NW, Rajendran VR, Alldredge SG, et al. Randomized comparison of Vasoseal and Angioseal closure devices in patients undergoing coronary angiography and angioplasty. *Catheter Cardiovasc Interv*. 2002;55:421–425.
16. Schulz-Schupke S, Helde S, Gewalt S, et al. Comparison of vascular closure devices vs manual compression after femoral artery puncture: the ISAR-CLOSURE randomized clinical trial. *JAMA*. 2014;312:1981–1987.
17. Bangalore S, Arora N, Resnic FS. Vascular closure device failure: frequency and implications: a propensity-matched analysis. *Circ Cardiovasc Interv*. 2009;2:549–556.
18. Klocker J, Gratl A, Chemelli A, et al. Influence of use of a vascular closure device on incidence and surgical management of access site complications after percutaneous interventions. *Eur J Vasc Endovasc Surg*. 2011;42:230–235.
19. Vaitkus PT. A meta-analysis of percutaneous vascular closure devices after diagnostic catheterization and percutaneous coronary intervention. *J Invasive Cardiol*. 2004;16:243–246.
20. Sanborn TA, Ebrahimi R, Manoukian SV, et al. Impact of femoral vascular closure devices and antithrombotic therapy on access site bleeding in acute coronary syndromes: The Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial. *Circ Cardiovasc Interv*. 2010;3:57–62.
21. Ahmed B, Piper WD, Malenka D, et al. Significantly improved vascular complications among women undergoing percutaneous coronary intervention: a report from the Northern New England Percutaneous Coronary Intervention Registry. *Circ Cardiovasc Interv*. 2009;2:423–429.
22. Marso SP, Amin AP, House JA, et al. Association between use of bleeding avoidance strategies and risk of periprocedural bleeding among patients undergoing percutaneous coronary intervention. *JAMA*. 2010;303:2156–2164.
23. Baklanov DV, Kim S, Marso SP, Subherwal S, Rao SV. Comparison of bivalirudin and radial access across a spectrum of preprocedural risk of bleeding in percutaneous coronary intervention: analysis from the national cardiovascular data registry. *Circ Cardiovasc Interv*. 2013;6:347–353.
24. Manolis AS, Pastromas S. Favorable single-operator experience with VasoSeal, a vascular closure device with extravascular collagen, in a large high-risk cohort of patients undergoing percutaneous coronary interventions. *Hosp Chronicles*. 2015;10:26–31.
25. Chamberlin JR, Lardi AB, McKeever LS, et al. Use of vascular sealing devices (VasoSeal and Perclose) versus assisted manual compression (Femostop) in transcatheter coronary interventions requiring abciximab (ReoPro). *Catheter Cardiovasc Interv*. 1999;47:143–147. discussion 148.

26. Silber S, Bjorvik A, Muhling H, Rosch A. Usefulness of collagen plugging with VasoSeal after PTCA as compared to manual compression with identical sheath dwell times. *Cathet Cardiovasc Diagn.* 1998;43:421–427.
27. Behan MW, Large JK, Patel NR, Lloyd GW, Sulke AN. A randomised controlled trial comparing the routine use of an Angio-Seal STS device strategy with conventional femoral haemostasis methods in a district general hospital. *Int J Clin Pract.* 2007;61:367–372.
28. Eggebrecht H, von Birgelen C, Naber C, et al. Impact of gender on femoral access complications secondary to application of a collagen-based vascular closure device. *J Invasive Cardiol.* 2004;16:247–250.
29. de Andrade PB, L.A EM, Tebet MA, et al. Design and rationale of the AngioSeal versus the Radial approach In acute coronary SyndromE (ARISE) trial: a randomized comparison of a vascular closure device versus the radial approach to prevent vascular access site complications in non-ST-segment elevation acute coronary syndrome patients. *Trials.* 2013;14:435.
30. Khan R, Ly HQ. Transradial percutaneous coronary interventions in acute coronary syndrome. *Am J Cardiol.* 2014;114:160–168.