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A Randomized Comparison of a Novel Bioabsorbable Vascular Closure Device Versus Manual Compression in the Achievement of Hemostasis After Percutaneous Femoral Procedures

The ECLIPSE (Ensure's Vascular Closure Device Speeds Hemostasis Trial)

S. Chiu Wong, MD,* William Bachinsky, MD,† Patrick Cambier, MD,‡ Robert Stoler, MD,§ Janah Aji, MD,‖ Jason H. Rogers, MD,¶ James Hermiller, MD,# Ravi Nair, MD,** Herbert Hutman, MD,†† Hong Wang, MD, MPH,†† for the ECLIPSE Trial Investigators

New York, New York; Harrisburg, Pennsylvania; Clearwater, Florida; Dallas, Texas; Camden and Warren, New Jersey; Sacramento, California; Indianapolis, Indiana; and Cleveland, Ohio

Objectives This trial compared the performance of a novel bioabsorbable vascular closure device (VCD) versus manual compression (MC) for access site hemostasis in patients undergoing percutaneous trans-femoral coronary or peripheral procedures.

Background From a patient's perspective, access site management after percutaneous procedures remains challenging.

Methods Patients enrolled in this multicenter, nonblinded trial underwent 6-F diagnostic or interventional procedures were randomly assigned 2:1 to VCD versus MC. The primary efficacy end points were time to hemostasis (TTH) and time to ambulation (TTA), and the primary safety end points were periprocedural and 30-day incidence of arterial access-related complications.

Results The trial assigned 401 patients (mean age 62.7 ± 10.9 years, 66.1% men) to VCD (n = 267) versus MC (n = 134) after 87 "roll-in" patients treated at 17 participating institutions. The baseline characteristics of the groups were similar. Procedural success was 91.8% in the VCD versus 91.0% in the MC group (p = NS). Mean TTH was 4.4 ± 11.6 min in the VCD versus 20.1 ± 22.5 min in the MC group (95% confidence interval: 19.0 to 12.3; $p < 0.0001$). Likewise, TTA was significantly shorter in the VCD (2.5 ± 5.0 h) than in the MC (6.2 ± 13.3 h) group (95% confidence interval: 5.5 to 1.9; p = 0.0028). No patient died or suffered a major access-site-related adverse event. Minor adverse events were few among all study groups.

Conclusions After 6-F percutaneous invasive procedures, TTH and TTA were both significantly shorter in patients assigned to VCD than in patients managed with MC. The 30-day rates of access-site-related complications were remarkably low in all groups. (Safety and Effectiveness Study of the Ensure Medical Vascular Closure Device; NCT00345631) (J Am Coll Cardiol Intv 2009;2:785–93)

From the *Weill Medical College of Cornell University, New York, New York; †Pinnacle Health at Harrisburg, Harrisburg, Pennsylvania; ‡Morton Plant Hospital, Clearwater, Florida; §Baylor Research Institute, Dallas, Texas; ‖Cooper Health Systems, Camden, New Jersey; ¶University of California, Davis Medical Center, Sacramento, California; #The Heart Center of Indiana, Indianapolis, Indiana; **University Hospitals of Cleveland, Cleveland, Ohio; and ††Cordis Corporation, Warren, New Jersey.
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From a patient's perspective, access site discomfort during sheath removal and periprocedural immobilization are some of the more exacting aspects of percutaneous vascular procedures. This has prompted the research and development of vascular closure devices (VCDs) to minimize discomfort and shorten the time to ambulation (TTA) after sheath removal, without compromising safety compared with traditional manual compression (MC).

In the past decade, a variety of VCDs have become available to facilitate the management of access sites after percutaneous vascular interventions (1). It was estimated that in 2007 VCDs were used to achieve hemostasis at the access site in approximately 30% of the nearly 10 million percutaneous vascular procedures performed in the U.S. (2). While most devices currently approved by the U.S. Food and Drug Administration have been associated, in multicenter randomized studies, with significantly shorter time to hemostasis (TTH) and TTA compared with standard manual or mechanical compression, their ease of use, patient comfort during deployment, and safety profiles are inconsistent.

Abbreviations and Acronyms

CI = confidence interval
MAE = major adverse event
MC = manual compression
TTA = time to ambulation
TTH = time to hemostasis
VCD = vascular closure device

The ExoSeal VCD (Cordis Corporation, Miami Lakes, Florida) was designed in an attempt to potentially address some of these deficiencies, and the ECLIPSE (Ensure's Vascular Closure Device Speeds Hemostasis Trial) study was carried out to compare its safety and effectiveness with that of MC in the promotion of hemostasis and early ambulation in patients undergoing percutaneous arterial, diagnostic, or interventional procedures.

Methods

The ECLIPSE trial was a randomized, nonblinded trial, conducted at 17 U.S. medical centers. Patients between 18 and 85 years of age, scheduled to undergo a diagnostic or interventional coronary or peripheral procedure, via arterial puncture of a ≥5-mm lumen diameter common femoral artery, using a standard 6-F, ≤11-cm long introducer sheath, were eligible for enrollment in the trial. Patients were excluded from the trial if they: 1) had sustained a myocardial infarction with ST-segment elevation ≤48 h before the catheterization procedure; 2) had uncontrolled hypertension at time of closure (blood pressure ≥180/110 mm Hg); 3) had symptomatic leg ischemia in the target vessel limb, or had undergone prior femoral vascular surgery or placement of a vascular graft at the target site; 4) had a history of bleeding or platelet disorder, or had been treated with a thrombin-specific anticoagulant or low-molecular-weight heparin ≤24 h before the catheterization procedure, or were heparinized and: a) were assigned to VCD and had a >250 s pre-closure activated clotting time in presence, or >300 s in absence of a glycoprotein IIb/IIIa inhibitor, or b) were assigned to MC and had a >180 s pre-closure activated clotting time; 5) required punctures of both femoral arteries; 6) had undergone prior closure of the target artery with any VCD or MC ≤30 days before the catheterization procedure; 7) had fluroscopically visible calcium, atherosclerotic disease, or stent ≤1 cm of the puncture site that would interfere with VCD plug placement; or 8) had a pre-existing systemic or cutaneous infection.

Device description. The ExoSeal VCD is a novel bioabsorbable device designed for the sealing of femoral artery puncture sites in patients who have undergone diagnostic or interventional procedures using a standard 6-F introducer sheath. The device achieves hemostasis by means of a visually guided deployment mechanism that delivers a bioabsorbable poly-glycolic acid "plug" atop the femoral artery, anchored by the neurovascular bundle sheath. The plug, which is entirely extravascular, is subsequently hydrolyzed into CO_2 and H_2O via the Kreb's cycle, over a 3-month period.

Study end points. The *primary efficacy end points* of the study were: 1) TTH, measured in minutes; and 2) TTA, measured in hours. Hemostasis was defined as no or minimal subcutaneous oozing and the absence of expanding or developing hematoma. TTH was measured from the time the introducer sheath was removed to the time hemostasis was achieved. TTA was defined as time the introducer sheath was removed to the time the patient was able to stand and walk ≥20 ft, without recurrence of bleeding. Patients not receiving glycoprotein IIb/IIIa inhibitors treated with the VCD were to first be evaluated for ambulation at 1 h post-hemostasis; similar patients treated with MC were to first be evaluated no later than 4 h, and thereafter as clinically indicated. Patients receiving glycoprotein IIb/IIIa inhibitors were to first be evaluated at 2 and 6 h, respectively. While patients were recommended to have their ambulatory status evaluated at the aforementioned times, ambulation was not required if contrary to the clinical judgment of the physician.

The *secondary efficacy end points* of the study were: 1) time-to-eligibility for hospital discharge, measured from the time of access site closure to the time when the patient was judged by the physician to be ready for discharge from the hospital; 2) time-to-hospital discharge, measured from the time of access site closure to the time of patient discharge; 3) procedure success, defined as hemostasis achieved by the assigned method, without occurrence of a closure-related major adverse event (MAE). A MAE was defined as: 1) need for vascular repair by surgical or nonsurgical techniques; 2) bleeding requiring a blood transfusion; 3) infection requiring antibiotics, extended hospitalization, or both; 4) new onset ischemia of the ipsilateral lower extremity; 5)

need for surgical repair of access-site-related nerve injury; or 6) permanent access site-related nerve injury. Device success was defined as: 1) the uncomplicated deployment of the plug; 2) hemostasis achieved in ≤5 min; and 3) removal of an intact delivery system.

The *primary safety end point* was the 30-day rate of combined arterial closure-related MAE. The *secondary safety end points* included multiple fatal or nonfatal post-procedural complications including: 1) recurrent local bleeding requiring a hemostatic intervention, or a ≥6-cm hematoma or ecchymosis; 2) development of pseudoaneurysm, arterio-venous fistula, vascular laceration, or retroperitoneal bleeding; 3) ipsilateral manifestations of vascular insufficiency or embolization, including loss of distal pulse, total arterial occlusion, or deep vein thrombosis; 4) infection; and 5) nerve injury.

Study protocol and data collection. The ECLIPSE study protocol was reviewed and approved by the institutional review committee of each participating medical institution, and all patients granted their informed consent to be included in the trial.

RANDOMIZATION PROCEDURE. At the completion of diagnostic or interventional procedures, femoral angiograms were obtained. Patients were then randomly assigned to VCD versus MC, using sealed envelopes in a 2:1 design favoring the VCD. The assignment was based on a computer-generated treatment list, which balanced the randomization by center and by type of procedure performed (coronary versus peripheral, and diagnostic versus interventional). An enrollment of at least 400 randomly assigned patients was planned, with at least 50% of patients undergoing an interventional procedure. In addition, a series of "roll-in" patients, treated with VCDs during the training period of each participating institution and not randomized, was included in a planned separate data collection and analysis.

The enrollment period of the trial lasted 6 months, and the patient clinical follow-up lasted 30 days. The data were collected by clinical coordinators at the clinical sites, and were managed and analyzed by an independent clinical research organization (Averion International Corp., Southborough, Massachusetts). Detailed information regarding the catheterization procedure, including the time from insertion of the procedural sheath to completion of the procedure and removal of procedural catheters, was recorded. A baseline duplex ultrasound examination of the target femoral artery closure site was performed before the index procedure in the first 25% of the overall sample population. After the procedure was completed, a femoral angiogram was performed and the activated clotting time was measured. At that point, if all the criteria for entry in the trial were satisfied, an envelope was opened to randomly assign the patient to VCD or MC stratified according to the type of procedure, interventional versus diagnostic, performed.

After the vessel closure procedure was completed, immediate effectiveness and safety end points were ascertained. All relevant adverse events were recorded, including recurrence of bleeding at the procedural site, which was treated by MC or other techniques to achieve hemostasis. On the day of discharge from the hospital, or on the day the patient was judged by the investigator to be ready for discharge from the hospital, a detailed assessment of medications, pedal pulse score, interim adverse events, and secondary safety measures was performed, and the access site was closely examined for abnormalities such as ecchymosis, swelling, mass, infection, or bruit.

FOLLOW-UP VISIT. Patients were scheduled to return for a follow-up visit (30-day visit) no earlier than 23 and no later than 37 days after the index procedure. At that time, the patient's interim medical history, clinical status, pedal pulse score, and occurrence of adverse events since hospital discharge were recorded. The access site was examined for abnormalities such as ecchymosis, swelling, mass, infection, or bruit. In addition, patients who had been selected for a baseline duplex ultrasound of the vascular access site underwent repeat ultrasound studies at the 30-day visit.

Procedural anticoagulation. The anticoagulation regimens prescribed in each study subgroup before, during, and after the index procedure were left to the discretion of each individual investigator. The numbers and percentages of patients treated with abciximab, aspirin, clopidogrel, eptifibatide, and heparin in each study group are shown in Table 1. It is noteworthy that in the groups assigned to VCD and MC, heparin was administered respectively to 94.7% and 94.1% of patients during interventional procedures, versus only 7.5% and 6.1% of patients during diagnostic procedures.

Study monitoring. An independent Clinical Events Committee (Online Appendix) adjudicated significant clinical events, and an independent Data and Safety Monitoring Committee (Online Appendix) reviewed the reported adverse events throughout the trial.

Statistical analyses. The data were analyzed on the intention-to-treat principle. The randomly assigned patient groups were analyzed separately from the "roll-in" group. For the effectiveness analysis, a sequential testing procedure was implemented, which assessed TTH first, followed by TTA if statistical significance was reached in the analysis of TTH. An unpaired t test with a 5% 2-sided type I error rate was used in both analyses. After confirming the statistical significance of the differences in both primary effectiveness end points between the randomly assigned groups, a noninferiority test with a 5% 1-sided type I error rate was applied to the primary safety end point of composite 30-day MAE, using a pre-specified noninferiority margin of 4%. The noninferiority p value was calculated using Cytel StatXact, version 6.0 (Cytel Inc., Cambridge, Massachusetts).

Table 1. Baseline Patient and Procedure Characteristics of the 3 Study Groups

	Roll-In (n = 87)	VCD (n = 267)	MC (n = 134)
Patient characteristics			
Age, yrs	63.3 ± 11.6	63.3 ± 11.1	61.4 ± 10.5
Women, n (%)	29 (33)	85 (32)	51 (38)
Body mass index 30 kg/m^2, n (%)	41 (47.1)	100 (37.4)	45 (33.6)
Baseline hematocrit, %	40.4 ± 4.2	41.4 ± 2.0	40.5 ± 4.4
History of: n (%) of patients			
Percutaneous coronary intervention	37 (42.5)	110 (41.2)	61 (45.5)
Coronary artery bypass graft	16 (18.4)	45 (16.9)	24 (17.9)
Peripheral vascular surgery or graft	4 (4.6)	8 (3.0)	1 (0.8)
Hyperlipidemia	70 (80.5)	211 (79.0)	117 (87.3)
Hypertension	70 (80.5)	206 (77.2)	98 (73.1)
Diabetes	21 (24.1)	68 (25.5)	44 (32.8)
Renal insufficiency	7 (8.1)	23 (8.6)	9 (6.7)
Smoking	39 (44.8)	152 (57.1)	66 (49.3)
Systolic blood pressure,* mm Hg	134 ± 22	133 ± 20	133 ± 20
Procedure characteristics			
Type of procedure, n (%) of patients			
Diagnostic	58 (66.7)	134 (50.2)	66 (49.3)
Interventional	29 (33.3)	133 (49.8)	68 (50.8)
Antithrombotic treatment, n (%) of patients†			
Abciximab	2 (2.3)	10 (7.5)	4 (5.9)
Aspirin	2 (2.3)	7 (5.3)	3 (4.4)
Clopidogrel	7 (8.0)	28 (21.1)	12 (17.6)
Eptifibatide	9 (10.3)	27 (10.1)	11 (8.2)
Heparin	37 (42.5)	136 (50.9)	68 (50.7)
Activated clotting time,* s	168 ± 55	181 ± 56	142 ± 34‡

Unless specified otherwise, values are mean ± SD. *Immediately before sheath removal; †among patients who underwent diagnostic procedures, none received abciximab or clopidogrel, and 1 patient each in the manual compression (MC) and vessel closure device (VCD) groups received eptifibatide; ‡p < 0.0001 versus VCD; all other differences between the 2 randomly assigned groups are statistically nonsignificant.

Besides the primary end points, the baseline patients and procedural characteristics and miscellaneous end points were also described, with calculations of means and standard deviation for continuous variables, and frequencies (in percentages) for categorical variables. When comparing groups assigned to VCD versus MC, Wilcoxon rank sum test and *t* test were applied for continuous and ordinal variables, and Fisher exact test for binary variables. Differences between 2 groups and 95% confidence intervals (CIs) of the differences were calculated. Statistical significance was declared when the 2-sided p value was <0.05. All statistical analyses were performed using the SAS statistical software, version 8.2 (SAS Institute, Cary, North Carolina) unless specified otherwise.

Results

Between February 2007 and August 2007, 401 patients were randomly assigned to either VCD (n = 267) or MC (n = 134), and 87 patients were included in the ECLIPSE trial as "roll-ins." Of the 401 randomly assigned patients, 200 (50%) underwent diagnostic and 201 underwent interventional procedures. The baseline demographic and clinical characteristics of the 3 study groups were similar (Table 1). The mean ages of the patients in the VCD, MC, and "roll-in" groups were 63.3 ± 11.1 years, 61.4 ± 10.5 years, and 63 ± 11.6 years, respectively (p = NS). Approximately two-thirds of patients in each group were men. The body mass index was >30 and ≤40 kg/m^2 in 37.4%, 33.6%, and 47.1% of patients in the VCD, MC, and "roll-in" groups, respectively (p = NS).

Effectiveness analysis. Procedural success, defined as hemostasis achieved by the assigned method without occurrence of a closure-related MAE on the day of procedure and at 30 days, was achieved in 245 of 267 patients (91.8%) assigned to VCD versus 122 of 134 patients (91%) assigned to MC (p = NS), and in 83 "roll-in" patients (95.4%). Device success, defined as uncomplicated deployment of the plug, removal of an intact delivery system, and hemostasis achieved in ≤5 min, was observed in 238 patients assigned to VCD (89.1%) and 83 "roll-in" patients (95.4%). In patients considered to have device failures, achievement of

hemostasis was >5 min in all patients, and plug deployment was unsuccessful in 21 of 33 patients. None of these patients suffered any closure-related MAE; however, 2 failures resulted in rebleeding at the site, 2 in hematomas < 6 cm, and 1 patient had an asymptomatic decrease in pedal pulse from grade 2 to 1.

The primary effectiveness end points could be evaluated in all 401 randomly assigned patients (Table 2). The mean TTH was 4.4 ± 11.6 min in the group assigned to VCD versus 20.1 ± 22.5 min in the group assigned to MC, corresponding to a 15.7 min difference (95% CI: 19.0 to 12.3; p < 0.0001). Likewise, TTA was significantly shorter in the group assigned to VCD (2.5 ± 5.0 h) than in the group assigned to MC (6.2 ± 13.3 h) corresponding to a 3.7 h difference (95% CI: 5.5 to 1.9; p = 0.0028).

Among the 401 randomly assigned patients, 200 underwent diagnostic and 201 underwent interventional procedures. Among the 200 patients who underwent diagnostic procedures, 134 were randomly assigned to VCD and 66 to MC. In addition, 58 "roll-in" patients underwent diagnostic procedures. Among the 201 randomly assigned patients who underwent interventional procedures, 133 were assigned to VCD and 68 to MC; interventional procedures were also performed in 29 "roll-in" patients. Table 3 shows the results of the primary effectiveness end points in these patient subgroups. As in the case of the overall population, both TTH and TTA were significantly shorter in patients assigned to VCD than in patients assigned to MC regardless whether patients underwent diagnostic or interventional procedures. While in the group assigned to MC, the mean TTH was significantly longer among patients who underwent interventional than among patients who underwent diagnostic procedures (25.2 ± 30.5 min vs. 14.8 ± 5.9 min, p = 0.008), this difference was not significant in the group assigned to VCD (5.4 ± 15.6 min vs. 3.3 ± 4.9 min, p = 0.143). Figure 1 compares the mean TTH and TTA between patients assigned to VCD and patients assigned to MC, who were treated with glycoprotein IIb/IIIa receptor blockers during the procedures. Both times were significantly shorter in the group assigned to VCD.

Study compliance and safety end points. Clinical follow-up was available at 30 days visit in 256 (95.9%), 126 (94.0%), and 84 (96.6%) patients assigned to VCD and MC, and in the "roll-in" group, respectively. No patient, in any group, died during the trial or experienced an arterial closure-related MAE, confirming the study hypothesis of noninferiority of the VCD compared with MC with respect to the primary safety end point. A few secondary safety adverse events occurred in each study group, without statistically significant differences among the groups or between the subgroups of patients who underwent diagnostic versus interventional procedures (Tables 2 and 3). Rebleeding after initial hemostasis (n = 17 of 382) and access site hematoma ≥6 cm (n = 7 of 382) were the most frequent adverse events

Table 2. Effectiveness and Safety Results in the 3 Study Groups

	Roll-Ins (n = 87)	VCD (n = 267)	MC (n = 134)	ΔVCD-MC (95% CI)	p Value*
Effectiveness measures					
Time to (mean ± SD)					
Hemostasis (min)	4.7 ± 19.4	4.4 ± 11.6	20.1 ± 22.5 (n = 131)	−15.7 (−19.0 to −12.3)	<0.0001
Ambulation (h)	2.0 ± 2.6	2.5 ± 5.0 (n = 264)	6.2 ± 13.3 (n = 129)	−3.7 (−5.5 to −1.9)	0.0028
Eligibility for hospital discharge (h)	9.7 ± 14.2 (n = 85)	12.6 ± 13.9 (n = 257)	16.3 ± 27.5 (n = 128)	−3.7 (−7.8 to 0.5)	0.1540
Hospital discharge (h)	13.6 ± 18.5	16.8 ± 19.8 (n = 264)	19.4 ± 29.2 (n = 133)	−2.6 (−7.5 to 2.3)	0.3612
Device deployment (min)	0.9 ± 1.1	1.0 ± 2.1 (n = 260)	—	—	—
Safety measures to 30 days	(n = 84)	(n = 256)	(n = 126)		
Major adverse events composite†	0	0	0	0 (0 to 1.05)	0.0005
Secondary safety composite end point	7 (8.3)	22 (8.5)	5 (4.0)	4.6 (−1.1 to 9.2)	0.1360
Rebleeding after initial hemostasis	3 (3.6)	14 (5.4)	3 (2.4)	3.1 (−1.8 to 6.9)	0.1989
Access site hematoma ≥6 cm	3 (3.6)	6(2.4)	1 (0.8)	1.6 (−2.2 to 4.3)	0.4334
Access site-related bleeding requiring >30 min for hemostasis	1 (1.2)	1 (0.4)	1 (0.8)	−0.4 (−4.0 to 1.5)	0.5503
Transient access site-related nerve injury	0	1 (0.4)	0	0.4 (−2.6 to 2.2)	1.0000
Retroperitoneal bleeding	0	2 (0.8)	0	0.8 (−2.2 to 2.8)	0.3298
Ecchymosis ≥6 cm	1 (1.2)	0	1 (0.8)	−0.8 (−4.4 to 0.8)	—
Decreased pedal pulse	1 (1.2)	0	0	—	—
Death	0	0	0	—	—

Unless specified otherwise, values indicate n (%) of patients. *The p value for primary safety end point was calculated from the noninferiority test between VCD and MC with a pre-specified noninferiority margin of 4.0%. The p values for the secondary end points were from Fisher exact test; †primary safety end point includes: 1) need for surgical or nonsurgical vascular repair; 2) access site-related: a) bleeding requiring transfusion, b) infection requiring antibiotics or extended hospitalization, c) nerve injury requiring surgery, d) >30 days nerve injury; and 3) new ipsilateral lower extremity ischemia.

CI = confidence interval; other abbreviations as in Table 1.

Table 3. Effectiveness and Safety Results in the 3 Study Subgroups Stratified by Diagnostic Versus Interventional Procedure

Effectiveness Measures	Roll-Ins	VCD	MC	ΔVCD-MC (95% CI)	p Value*
Diagnostic procedures	(n = 58)	(n = 134)	(n = 66)		
Time to (mean ± SD)					
Hemostasis (min)	2.7 ± 2.8	3.3 ± 4.9	14.8 ± 5.9 (n = 65)	−11.5 (−13.0 to −9.9)	<0.0001
Ambulation (h)	1.4 ± 0.8	1.6 ± 1.2 (n = 133)	6.6 ± 18.4	−5.0 (−8.2 to −1.9)	0.0295
Eligibility for hospital discharge (h)	5.4 ± 14.8 (n = 57)	4.9 ± 7.4 (n = 131)	11.9 ± 35.4 (n = 64)	−7.0 (−13.3 to −0.6)	0.1257
Hospital discharge (h)	9.7 ± 21.4	8.7 ± 20.2 (n = 132)	14.8 ± 38.8 (n = 65)	−6.1 (−14.3 to 2.2)	0.2402
Device deployment (min)	1.0 ± 1.3	1.2 ± 2.9 (n = 131)	—	—	—
30-day major adverse events composite†	0	0	0	0 (0 to 1.99)	0.0091
Interventional procedures	(n = 29)	(n = 133)	(n = 68)		
Time to (mean ± SD)					
Hemostasis (min)	8.6 ± 33.4	5.4 ± 15.6	25.2 ± 30.5 (n = 66)	19.8 (−26.2 to −13.4)	<0.0001
Ambulation (h)	3.10 ± 4.17	3.5 ± 6.9 (n = 131)	5.8 ± 3.5 (n = 63)	−2.3 (−4.1 to −0.5)	0.0022
Eligibility for hospital discharge (h)	18.4 ± 6.9 (n = 28)	20.5 ± 14.7 (n = 126)	20.6 ± 15.2 (n = 64)	−0.2 (−4.7 to 4.3)	0.9460
Hospital discharge (h)	21.6 ± 5.1	24.8 ± 15.8 (n = 132)	23.7 ± 14.4	1.1 (−3.4 to 5.6)	0.6270
Device deployment (min)	0.9 ± 0.8	0.8 ± 0.8 (n = 129)	—	—	—
30-day major adverse events composite†	0	0	0	0 (0 to 2.00)	0.0093

Unless specified otherwise, values indicate numbers (%) of patients. *The p value for the primary safety end point was calculated from the noninferiority test between VCD and MC with a pre-specified noninferiority margin of 4.0%; †primary safety end point includes: 1) need for surgical or nonsurgical vascular repair; 2) access site-related: a) bleeding requiring transfusion, b) infection requiring antibiotics or extended hospitalization, c) nerve injury requiring surgery, d) >30 days nerve injury; and 3) new ipsilateral lower extremity ischemia.
CI = confidence interval; other abbreviations as in Table 1.

observed in both the randomized VCD and the MC groups. Two patients who underwent interventional procedures in the VCD group suffered from retroperitoneal bleeding documented by computed tomography scan. One patient experienced transient decrease in blood pressure after device deployment and responded promptly with fluid without transfusion. His hematocrit decreased from 43.7% to 32.1%. A second patient complained of groin discomfort 2 h after the procedure, and a small localized swelling was noted on routine groin evaluation. His hematocrit dropped from 33.6% to 25.4%. Neither patient had documented back pain, prolonged hypotension, required a blood transfusion or vascular repair. The first patient was discharged 28 h and the second at 96 h after the procedure.

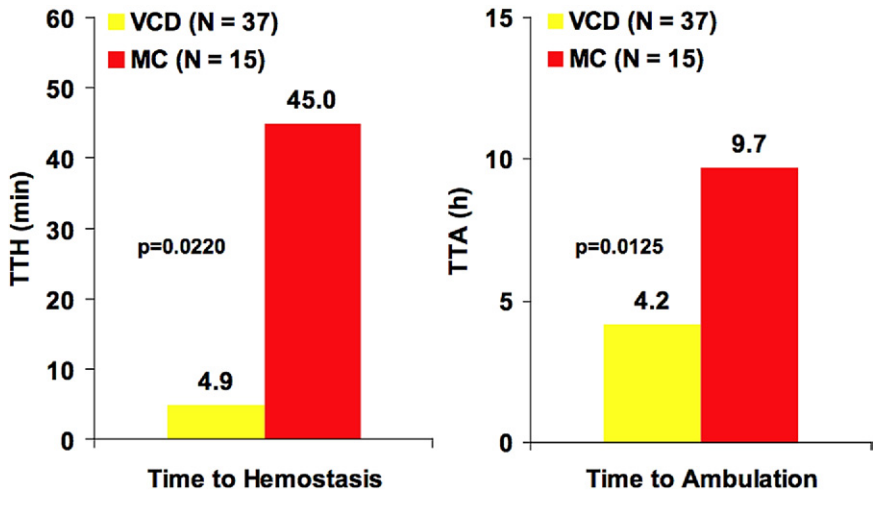

Figure 1. TTH and TTA in Patients Treated With Glycoprotein IIb/IIIa Receptor Blocker

In the subgroup of patients who received glycoprotein IIb/IIIa receptor blocker during their procedures, there was a significant reduction in both the mean time to hemostasis (TTH) **(left)** and time to ambulation (TTA) **(right)** in patients assigned vessel closure device (VCD) compared with patients assigned to manual compression (MC).

Duplex ultrasonographic observations. Pre-procedural duplex ultrasound of the target femoral artery was obtained in 67 patients assigned to VCD and 33 patients assigned to MC. The studies were technically satisfactory in 98.5% and 100% of patients, respectively. Turbulent blood flow or signs of partial vascular obstruction were observed in 4 patients (6.0%) in the VCD group and 2 patients (6.1%) in the MC group before index procedure. The duplex ultrasound studies were repeated at the 30-day visit in 62 patients in the VCD group and 32 patients in the MC group, and were technically satisfactory in 100% of patients. Turbulent blood flow or signs of partial vascular obstruction were observed in 4 patients (6.5%) in the VCD group and 1 patient (3.1%) in the MC group. The patients with follow-up ultrasound abnormalities were not the same as those with abnormal baseline studies. These between-group differences were all statistically nonsignificant. It is particularly noteworthy that no pseudo-aneurysm, arterio-venous fistula, or hematoma was observed on 30-day follow-up ultrasound examination in either study group.

Discussion

Impetus for the development of VCDs. In patients undergoing diagnostic or interventional procedures, all currently available VCDs shorten TTH and TTA significantly when compared with MC. This effect is generally beneficial, particularly in patients presenting with chronic back pain, congestive heart failure, prostate enlargement, mental impairment, or other disorders that preclude prolonged bed rest after the procedure.

Despite substantial improvements in device design and gains in operator experience over the past decade, VCDs were deployed in only 30% of the estimated 10 million percutaneous vascular procedures performed in the U.S. in 2007 (2). This underutilization of VCDs for the management of access site hemostasis after percutaneous procedures is clearly multifactorial, including costs of materials, ease of use, and lack of definitive evidence that VCDs are at least as safe as MC when applied to a variety of anatomical sites and clinical states.

Safety of current VCDs. Since VCDs are often deployed in fully anticoagulated patients after percutaneous interventional procedures, bleeding complications in these patients are potentially more serious than with MC, where removal of the sheath is usually postponed until normal clotting status has returned. In recent analyses and meta-analyses of single- and multicenter clinical trials, bleeding complications associated with percutaneous interventions were not only costly (3), but also a predictor of poor prognosis and increased short- and long-term mortality (4–9).

Concerns regarding the safety of VCDs have prompted 2 consecutive U.S. Food and Drug Administration reviews, using the American College of Cardiology–National Cardiovascular Data Registry (10,11). The combined results of both studies suggest that the overall safety in patients treated with VCDs and MC is similar, with the exception of a greater risk of major local vascular complications after cardiac catheterization observed with the VasoSeal device (Datascope Corp., Montvale, New Jersey) (11). In a meta-analysis of 16 randomized clinical studies comparing the rates of access site complications (excluding hematoma) associated with VCDs versus MC in over 5,000 patients, Vaitkus (12) reported a lower risk of vascular complications associated with VCD. As was confirmed by Tavris et al. (11), the VasoSeal VCD performed less well than other devices. Two other meta-analyses comparing the safety of VCD with MC, published in 2004 (13,14), found similar rates of periprocedural, access site complication with VCD and MC, whether the procedure was diagnostic or interventional. Furthermore, in the meta-analysis by Nikolsky et al. (14), the overall complication rate in the setting of interventional procedures was significantly higher with the VasoSeal VCD than with MC. Finally, in the meta-analysis by Koreny et al. (13), as in this study, TTH was significantly shorter with the use of VCD than when MC was applied.

In 2002, Applegate et al. (15) observed lower rates of vascular complications than reported in the previous decade, which they attributed, among other factors, to less vigorous antithrombotic therapy and greater operator experience. Other single-center studies have confirmed the effectiveness of access site management with VCD, including in higher risk subgroups, such as women (16) and patients treated with glycoprotein IIb/IIIa inhibitors (17). In addition, in a very recent analysis of a prospective registry, which enrolled nearly 13,000 consecutive patients in the years 2002 through 2007, Arora et al. (18) found significantly lower rates of vascular complications with the use of VCD than with MC in "appropriately selected patients undergoing diagnostic and therapeutic cardiac catheterizations." Furthermore, using a second-order Monte Carlo simulation model, Resnic et al. (3) found that the routine use of a VCD was more cost effective than MC in a recent case-control analysis of nearly 4,000 patients who underwent percutaneous coronary interventions.

The ExoSeal device. Currently available VCDs could certainly be further improved. The device used in this study has several favorable design characteristics. In particular, the poly-glycolic acid material that constitutes the "felt like" plug is synthetic, eliminating the potential adverse effect(s) associated with animal-based components. Once deployed, the hemostatic plug is entirely extravascular, with no intravascular components. It is completely absorbed within 3 months through a noninflammatory hydrolysis process via the Kreb's cycle, which might: 1) lessen scarring of the access site; 2) enhance the safety of its use; and 3) facilitate subsequent re-entries at the same access site. The device uses the existing arterial sheath as the conduit for its

deployment, minimizing the need for widening of the track through the tissues, and eliminating maneuvers that may cause discomfort at the femoral access site during its deployment. In contrast to all currently available VCD, the deployment of this device depends mostly on visual rather than on tactile cues. The unique, visually guided deployment mechanism eliminates the obligatory push and tug steps, which are usually associated with greater patient discomfort.

The ECLIPSE trial. This trial showed that the study device was effective when used in patients undergoing coronary or peripheral, diagnostic or interventional procedures, using 6-F instrumentation. No major access site complication was observed in either study group, and the device was deployed within approximately 1 min. Compared with MC, TTH and TTA were markedly shorter in patients treated with the VCD, despite the performance of percutaneous coronary interventions in nearly 50% of patients, and the intraprocedural administration of glycoprotein IIb/IIIa inhibitors in over 10% of patients. In patients who underwent diagnostic procedures and were randomly assigned to VCD, in contrast with MC, no significant difference in TTH was observed between patients who underwent diagnostic and interventional procedures.

Retroperitoneal hemorrhages occurred in 2 patients who had undergone interventional procedures in the VCD group. Neither patient required surgical or percutaneous interventions, or blood transfusions. Whether the rate of secondary complications associated with the use of VCD observed in this trial will decrease overtime with more refined operator experience remains to be determined.

Study limitations. As mandated by the protocol, patients with femoral arterial disease, moderate calcifications at the site of sheath insertion, or whose femoral artery was cannulated within the prior 30 days were excluded from the trial. Therefore, the performance of this VCD in these more "real-world" clinical settings still needs to be studied and compared with that of other currently available devices.

Despite the roll-in patients, the total number of patients enrolled per site is relatively small minimizing the benefit of a learning curve with this VCD technique. In addition, patient satisfaction and cost effectiveness of ExoSeal compared with MC and other VCDs was not examined in the current study. Future clinical studies to further assess whether the design advantages of ExoSeal, with its extravascular noninflammatory plug and unique visually guided deployment mechanism, will translate into significant improvements in clinical outcomes over the currently available VCDs are clearly warranted.

Conclusions

In this study of patients at standard risk for the use of a VCD, the ExoSeal device after interventional or diagnostic procedures with 6-F instrumentation in coronary and peripheral vessels was associated with a marked shortening of TTH and TTA, and with rates of access site complications similar to those observed with MC. No major complication was observed during the trial in any study group. Follow-up ultrasound examinations performed at 30 days in 25% of the sample population revealed no abnormality at the access site.

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Reprint requests and correspondence: Dr. S. Chiu Wong, New York Presbyterian Hospital, 525E 68th Street, F433 Box 108, New York, New York 10065. E-mail: scwong@med.cornell.edu.

REFERENCES

1. Dauerman HL, Applegate RJ, Cohen DJ. Vascular closure devices: the second decade. J Am Coll Cardiol 2007;50:1617–26.
2. Turi ZG. An evidence-based approach to femoral arterial access and closure. Rev Cardiovasc Med 2008;9:6–18.
3. Resnic FS, Arora N, Matheny M, Reynolds MR. A cost-minimization analysis of the angio-seal vascular closure device following percutaneous coronary intervention. Am J Cardiol 2007;99:766–70.
4. Kinnaird TD, Stabile E, Mintz GS, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. Am J Cardiol 2003;92:930–5.
5. Segev A, Strauss BH, Tan M, Constance C, Langer A, Goodman SG, Canadian Acute Coronary Syndromes Registries Investigators. Predictors and 1-year outcome of major bleeding in patients with non–ST-elevation acute coronary syndromes: insights from the Canadian Acute Coronary Syndrome registries. Am Heart J 2005;150:690–4.
6. Yatskar L, Selzer F, Feit F, et al. Access site hematoma requiring blood transfusion predicts mortality in patients undergoing percutaneous coronary intervention: data from the National Heart, Lung, and Blood Institute Dynamic registry. Catheter Cardiovasc Interv 2007;69:961–6.
7. Manoukian SV, Feit F, Mehran R, et al. Impact of major bleeding on 30-day mortality and clinical outcomes in patients with acute coronary syndromes: an analysis from the ACUITY trial. J Am Coll Cardiol 2007;49:1362–8.
8. Feit F, Voeltz MD, Attubato MJ, et al. Predictors and impact of major hemorrhage on mortality following percutaneous coronary intervention from the REPLACE-2 trial. Am J Cardiol 2007;100:1364–9.
9. Ndrepepa G, Berger PB, Mehilli J, et al. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. J Am Coll Cardiol 2008;51:690–7.
10. Tavris DR, Gallauresi BA, Lin B, et al. Risk of local adverse events following cardiac catheterization by hemostasis device use and gender. J Invasive Cardiol 2004;16:459–64.
11. Tavris DR, Dey S, Albrecht-Gallauresi B, et al. Risk of local adverse events following cardiac catheterization by hemostasis device use—phase II. J Invasive Cardiol 2005;17:644–50.
12. Vaitkus PT. A meta-analysis of percutaneous vascular closure devices after diagnostic catheterization and percutaneous coronary intervention. J Invasive Cardiol 2004;16:243–6.
13. Koreny M, Riedmüller E, Nikfardjam M, Siostrzonek P, Müllner M. Arterial puncture closing devices compared with standard manual compression after cardiac catheterization: systematic review and meta-analysis. JAMA 2004;291:350–7.
14. 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;44:1200–9.
15. Applegate RJ, Grabarczyk MA, Little WC, et al. Vascular closure devices in patients treated with anticoagulation and IIb/IIIa receptor inhibitors during percutaneous revascularization. J Am Coll Cardiol 2002;40:78–83.
16. Ratnam LA, Raja J, Munneke GJ, Morgan RA, Belli AM. Prospective nonrandomized trial of manual compression and Angio-Seal and Starclose arterial closure devices in common femoral punctures. Cardiovasc Intervent Radiol 2007;30:182–8.
17. Resnic FS, Blake GJ, Ohno-Machado L, Selwyn AP, Popma JJ, Rogers C. Vascular closure devices and the risk of vascular complications after percutaneous coronary intervention in patients receiving glycoprotein IIb-IIIa inhibitors. Am J Cardiol 2001;88:493–6.
18. Arora N, Matheny ME, Sepke C, Resnic FS. A propensity analysis of the risk of vascular complications after cardiac catheterization procedures with the use of vascular closure devices. Am Heart J 2007;153:606–11.

Key Words: hemostasis ■ vascular closure ■ manual compression ■ percutaneous intervention ■ arterial puncture.

APPENDIX

For a list of the the study investigators and institutions, please see the online version of this article.