A Prospective, Randomized, Pivotal Trial of a Novel Extravascular Collagen-Based Closure Device Compared to Manual Compression in Diagnostic and Interventional Patients

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ABSTRACT: Objectives. The RESPECT trial was aimed at evaluating safety/efficacy of a new extravascular closure system in diagnostic (Dx) and interventional (Ix) procedures performed through 6 or 7 Fr introducer sheaths. **Background.** Although vascular closure devices (VCDs) have been available for two decades, manual compression (MC) remains the standard of care in many institutions. VCDs have not been shown to have greater safety than MC. **Methods.** The RESPECT trial was a multicenter, randomized comparison of the Vascade VCD (Cardiva Medical, Inc) versus MC in Dx and Ix patients undergoing femoral access. Endpoints included time to hemostasis (TTH), time to ambulation (TTA), time to discharge eligibility (TTDe), device and procedure success, major and minor complications. Subjects were randomized 2:1 (Vascade vs MC). **Results.** A total of 420 patients were enrolled (211 Dx, 209 Ix). Mean age was 62 ± 11 years and 29% were female. For Ix Vascade/MC patients, 77%/69% received bivalirudin, 27%/26% received heparin, and 8%/3% received glycoprotein IIb/IIIa inhibitors, respectively. Patients were followed for 30 ± 7 days. A total of 415 subjects (98.8%) completed follow-up. TTH was 3.0 minutes (range, 0.6-31.6 minutes) for Vascade vs 20.0 minutes (range, 0.0-97.0 minutes) for MC; TTA was 3.2 hours (range, 1.0-78.0 hours) for Vascade vs 5.2 hours (range, 1.7-22.8 hours) for MC; and TTDe was 3.6 hours (range, 1.4-78.4 hours) for Vascade vs 5.7 hours (range, 2.2-23.2 hours) for MC. Device and procedure success rates were 98% for Vascade and 100% for MC. Minor events were 1.1% for Vascade and 7% for MC. No major access-site related complications were reported in either arm. **Conclusion.** Despite high percentage of bivalirudin use, there were no major access-site related complications in either arm. Vascade use reduced rates of minor access-site related complications, and significantly shortened TTH, TTA, and TTDe compared to MC.

J INVASIVE CARDIOL 2015;27(3):129-136

KEY WORDS: vascular closure devices, hemostasis, manual compression, vascular complications

It is expected that over 10 million cardiac catheterization procedures will be performed worldwide in 2013. Manual compression (MC) continues to be the standard of care (SOC) for achieving hemostasis after femoral puncture and is estimated to comprise approximately 60% of all closures with these procedures.[1] MC is perceived as simple, safe, and relatively inexpensive in spite of being time-consuming, resource intensive, and uncomfortable for the patient.

Meta-analyses of first- and second-generation vascular closure device (VCD) results continue to challenge the benefit of using VCDs and suggest that the risk versus benefit advantage has not been definitively demonstrated.[2,3] Prior devices have demonstrated that the time to hemostasis (TTH) is substantially lower with diagnostic angiography and transcatheter intervention with the use of VCDs. Furthermore, shorter TTH has the potential to facilitate recovery with a concomitant decrease in treatment costs. However, VCD use has not been shown to reduce complication rates. Moreover, first-generation devices increased the risk of serious arterial complications associated with the VCDs, including arterial stenosis, lower limb ischemia, infection, and other vascular injuries requiring surgical repair.[2]

These issues motivated the development of next-generation devices that are designed to deliver extravascular and biodegradable implants. This approach has solved many of the earlier issues by potentially reducing the incidence of vessel stenosis and embolism. However, these extravascular devices have suffered from increased bleeding and other minor complications and often require adjunctive MC with resulting increases in patient management time and potential delays in ambulation and discharge.[4-11]

The Vascade Vascular Closure System (Cardiva Medical) is new, next-generation extravascular technology that consists of a bioresorbable thrombogenic collagen patch. The device is compatible with 5, 6, or 7 Fr introducer sheaths and consists of an expandable nitinol disk that locates the vessel wall and provides temporary hemostasis and a retractable/lockable sleeve that houses a bovine-derived collagen patch. At the completion of the procedure, the Vascade device is inserted through the existing introducer sheath, the disk is deployed in the lumen of the artery, the sheath is removed over the device, and the disc is brought against the vessel wall to achieve temporary hemostasis. The protective sleeve

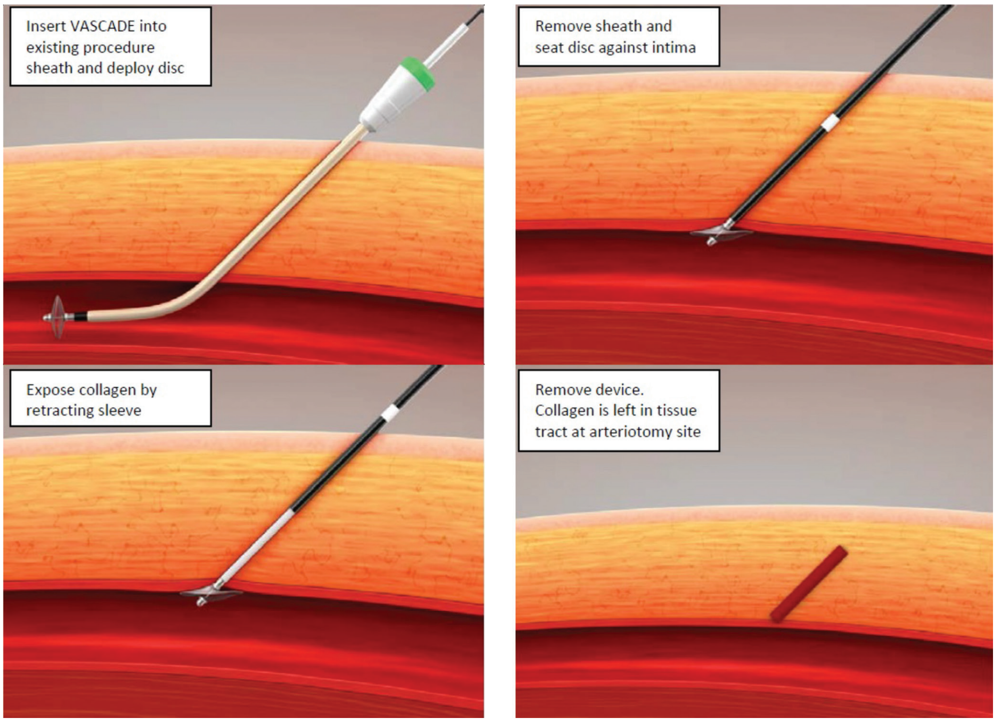

FIGURE 1. Vascade device deployment.

is unlocked and retracted, exposing the collagen patch in the tissue tract at the arteriotomy site. The disk is collapsed and the device is removed, leaving only the collagen patch behind in the tissue tract. There are no intravascular components. The patch expands upon exposure of collagen to blood and surrounding tissue fluid, filling the tissue tract and promoting coagulation and hemostasis (Figure 1).

The objective of the RESPECT trial was to demonstrate the safety and effectiveness of the Vascade VCS in sealing femoral arterial access sites following diagnostic or interventional endovascular procedures performed through 6 or 7 Fr introducer sheaths.

Methods

The RESPECT trial was a prospective, multicenter, randomized, open-label, controlled clinical trial designed to evaluate the safety and effectiveness of the Vascade 6/7 Fr VCS in sealing femoral arterial access sites and was specifically designed to demonstrate facilitated hemostasis, ambulation, and eligibility for hospital discharge, in comparison to manual compression (MC). Subjects were randomly assigned in a 2:1 ratio (Vascade to MC). Randomization was stratified by investigational site and procedure type (diagnostic vs interventional). Half of the subjects enrolled were to undergo interventional procedures. Study design, including inclusion and exclusion criteria, definitions of all major and minor safety, and primary and secondary effectiveness outcomes were approved by the United States (US) Food and Drug Administration and were largely consistent with previous VCD studies intended for market approval.

The *study population* was defined as patients undergoing cardiac or peripheral diagnostic or interventional catheterization procedures via the femoral artery approach when using a standard 6 Fr or 7 Fr introducer sheath. Measures of safety and efficacy were assessed through hospital discharge and 30 ± 7 days post procedure. The study was conducted at 20 US institutions and one Australian center. Patients were excluded if they had severe coexisting morbidities, including systemic infections, immunodeficiency, bleeding diathesis, extreme morbid obesity (body mass index >45), previous vascular grafts or surgery at the target site, and other ipsilateral arteriotomy or artery closure using permanent implant-based closure devices.

Patients that met the preoperative inclusion/exclusion criteria were invited to participate in the trial and sign the study-specific, Institutional Review Board/Ethics Committee (IRB/EC)-approved informed consent form before any study-specific tests or procedures were performed. All patients were scheduled to return for follow-up examinations at 30 ± 7 days post procedure. Post procedure, patients were evaluated for any major or minor complications or adverse events, including bleeding, neurological, and other potential device- or procedure-related adverse effects.

The primary safety endpoint was the rate of combined major access-site related complications within 30 ± 7 days following the catheterization procedure. These complications included: access-site related bleeding requiring transfusion; vascular injury requiring repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent graft); new ipsilateral lower-extremity ischemia causing a threat to the viability of the limb and requiring surgical or additional percutaneous intervention; access-site related infection requiring intravenous antibiotics and/or extended hospitalization; new-onset access-site related neuropathy in the ipsilateral lower extremity requiring surgical repair; and permanent access-site related nerve injury.

The secondary safety endpoint was the rate of combined minor access-site related complications within 30 ± 7 days following the procedure. Minor complications included: access-site related bleeding requiring >30 minutes to achieve hemostasis; access-site related hematoma >6 cm; late access-site

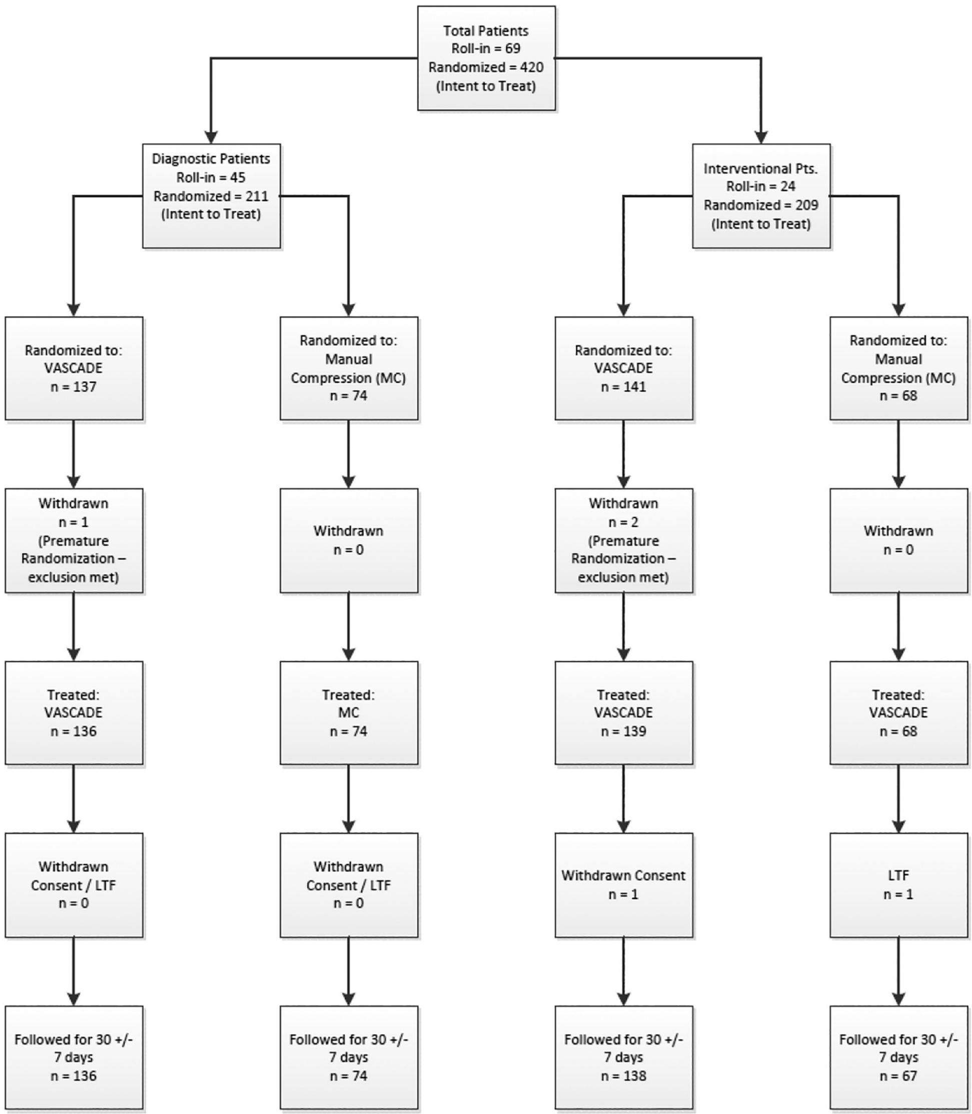

FIGURE 2. CONSORT Diagram providing patient accountability.

when subject stands and walks 20 feet without evidence of arterial bleeding from the access site, and *TTDe*, defined as elapsed time between device/sheath removal and when subject is medically able to be discharged based solely on access-site assessment. With regard to success/failure criteria, *procedure success* (defined as attainment of final hemostasis using any method and freedom from major vascular complications through 30 days), and *device success* (defined as the ability to deploy the delivery system, deliver the collagen, and achieve hemostasis with the Cardiva Vascade VCS alone or with adjunctive compression), were evaluated as additional secondary effectiveness measures.

An independent Clinical Events Committee (CEC) and a Data Safety Monitoring Board (DSMB, which was also designated as the Data Safety Monitoring Committee or DSMC) were responsible for systematic review and adjudication of any reported deaths, major and minor access-site related complications, and all potential device- or procedure-related adverse events (ie, events eligible for review).

related bleeding (following hospital discharge); ipsilateral lower-extremity arterial emboli; ipsilateral deep vein thrombosis; access-site related vessel laceration; access-site wound dehiscence; localized access-site infection treated with intramuscular or oral antibiotics; arteriovenous fistula not requiring treatment; pseudoaneurysm requiring thrombin injection or fibrin adhesive injection; pseudoaneurysm not requiring treatment; new-onset access-site related neuropathy in the ipsilateral lower extremity not requiring surgical repair; and ipsilateral pedal pulse diminished by two grades or transiently lost.

The primary effectiveness endpoint was *TTH*, which was strictly defined as the elapsed time between "device" removal (Vascade VCS removal for treatment arm and sheath removal for MC control arm), and first observed and confirmed arterial hemostasis. The secondary effectiveness endpoints were *TTA*, defined as elapsed time between device/sheath removal and

Results

Between September 2011 and June 2012, a total of 420 subjects were randomly assigned to treatment with either Vascade or MC. The randomized Vascade arm enrolled 137 diagnostic (Dx) and 141 interventional (Ix) subjects, while the MC arm enrolled 74 Dx and 68 Ix subjects at 20 US sites and one Australian site. A CONSORT diagram is provided in Figure 2.

The baseline demographic and clinical characteristics of the two treatment groups were very similar. The mean ages in the Vascade and MC groups were 61.8 ± 11.2 years, and 62.5 ± 10.4 years, respectively. The percentage of female subjects (29%) and the mean body mass index (30.2 kg/m^2) were identical in the two treatment groups. Table 1 provides a summary of the patient demographics. Baseline medical history and risk factors

Table 1. Demographics.

	Diagnostic (n = 211)		Interventional (n = 209)		Total (n = 420)		
	Vascade (n = 137)	MC (n = 74)	Vascade (n = 141)	MC (n = 68)	Vascade (n = 278)	MC (n = 142)	*P*-Value
Age (years)							
Number	136	74	139	68	275	142	
Mean	62.2 ± 11.8	62.8 ± 11.1	61.4 ± 10.6	62.3 ± 9.7	61.8 ± 11.2	62.5 ± 10.4	.51
Median	64 (30-80)	65 (34-79)	64 (36-80)	63.5 (40-79)	64 (30-80)	64 (34-79)	
Gender							
Number	136	74	139	68	275	142	
Female	48 (35%)	27 (36%)	31 (22%)	14 (21%)	79 (29%)	41 (29%)	>.99
Ethnicity							
Number	136	74	139	68	275	142	
Not Hispanic or Latino	125 (92%)	62 (84%)	127 (91%)	65 (96%)	252 (92%)	127 (89%)	
Hispanic or Latino	4 (3%)	7 (9%)	10 (7%)	3 (4%)	14 (5%)	10 (7%)	.73
Unknown	7 (5%)	5 (7%)	2 (1%)	0 (0%)	9 (3%)	5 (4%)	
Race							
Number	136	74	139	68	275	142	
White	120 (88%)	66 (89%)	129 (93%)	64 (94%)	249 (91%)	130 (92%)	
Black or African American	10 (7%)	4 (5%)	8 (6%)	2 (3%)	18 (7%)	6 (4%)	
American Indian or Alaska Native	3 (2%)	3 (4%)	1 (1%)	1 (1%)	4 (1%)	4 (3%)	
Other	2 (1%)	1 (1%)	0 (0%)	1 (1%)	2 (1%)	2 (1%)	.86
Asian	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	
Unknown	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	0 (0%)	

Data presented as number, mean ± standard deviation, or median (range). MC = manual compression.

were also very similar for the two treatment groups (Table 2). There were no statistically significant differences detected between the treatment and control groups in either baseline demographics or medical history.

Preprocedure anticoagulant and/or antiplatelet administration was reported in 81% of Vascade and 83% of MC cases. This included aspirin (76% Vascade/77% MC) and aspirin + clopidogrel (32% Vascade/24% MC). In the randomized Ix cohort, periprocedural bivalirudin was administered in 77% of Vascade cases and 69% of MC cases. Alternately, periprocedural heparin was administered in 27% of Vascade cases and 26% of MC cases. Periprocedural glycoprotein IIb/IIIa inhibitors were reportedly administered in 8% of Vascade cases and 3% of MC cases.

Activated clotting times (ACTs) were collected at the end of the catheterization procedure in subjects receiving unfractionated heparin. The mean ACTs in Ix subjects were similar among the groups, with 289.5 ± 136.9 seconds in the Vascade group vs 289.0 ± 100.7 seconds in the MC group. Mean ACT for Dx patients was 221 ± 68.7 seconds for the Vascade group and 171.8 ± 16.8 seconds for the MC group.

Table 3 shows the results of the primary and secondary effectiveness endpoints by treatment group and procedure type. On an intention-to-treat basis and according to protocol definitions, the mean TTH was 4.8 ± 5.4 minutes in the Vascade group vs 21.4 ± 12.4 minutes in the MC group ($P<.001$). For the Dx patients, the mean TTH was 4.0 ± 4.2 minutes in the Vascade group vs 18.2 ± 8.1 minutes in the MC group ($P<.001$). For the Ix patients, the mean TTH was 5.5 ± 6.3 minutes in the Vascade group vs 24.9 ± 15.1 minutes in the MC group ($P<.001$).

Mean TTA was significantly shorter in the group assigned to Vascade (3.8 ± 5.1 hours) than in the group assigned to MC (5.8 ± 3.1 hours; $P<.001$). Ambulation was achieved in ≤5 hours in 93% of all randomized Vascade subjects and in 48% of MC subjects. The mean TTDe was significantly shorter in the group assigned to Vascade (4.8 ± 6.4 hours) than in the group assigned to MC (6.5 ± 3.3 hours; $P<.01$). Discharge eligibility was achieved in ≤6 hours in 90% of the

Table 2. Medical history and risk factors.

	Diagnostic (n = 211)		Interventional (n = 209)		Total (n = 420)		
	Vascade (n = 137)	MC (n = 74)	Vascade (n = 141)	MC (n = 68)	Vascade (n = 278)	MC (n = 142)	*P*-Value
Hypercholesterolemia							
Number	136	74	139	68	275	142	
Yes	115 (85%)	56 (76%)	118 (85%)	59 (87%)	233 (85%)	115 (81%)	.33
No	21 (15%)	16 (22%)	21 (15%)	9 (13%)	42 (15%)	25 (18%)	
Unknown	0 (0%)	2 (3%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	
Hypertension							
Number	136	74	139	68	275	142	
Yes	102 (75%)	56 (76%)	114 (82%)	53 (78%)	216 (79%)	109 (77%)	.71
No	34 (25%)	18 (24%)	25 (18%)	15 (22%)	59 (21%)	33 (23%)	
Premature atherosclerotic disease							
Number	136	74	139	68	275	142	
Yes	48 (35%)	25 (34%)	78 (56%)	38 (56%)	126 (46%)	63 (44%)	.84
No	86 (63%)	48 (65%)	61 (44%)	29 (43%)	147 (53%)	77 (54%)	
Unknown	2 (1%)	1 (1%)	0 (0%)	1 (1%)	2 (1%)	2 (1%)	
Premature atherosclerotic disease in family							
Number	136	74	139	68	275	142	
Yes	58 (43%)	28 (38%)	56 (40%)	30 (44%)	114 (41%)	58 (41%)	.23
No	56 (41%)	34 (46%)	56 (40%)	33 (49%)	112 (41%)	67 (47%)	
Unknown	22 (16%)	12 (16%)	27 (19%)	5 (7%)	49 (18%)	17 (12%)	
Cigarette smoker							
Number	133	73	138	68	271	141	
Never	60 (45%)	33 (45%)	69 (50%)	24 (35%)	129 (48%)	57 (40%)	.28
Former	54 (41%)	31 (42%)	54 (39%)	29 (43%)	108 (40%)	60 (43%)	
Current	19 (14%)	9 (12%)	15 (11%)	15 (22%)	34 (13%)	24 (17%)	
GI/GU bleeding							
Number	136	74	139	68	275	142	
Yes	3 (2%)	0 (0%)	2 (1%)	0 (0%)	5 (2%)	0 (0%)	.17
No	133 (98%)	73 (99%)	137 (99%)	68 (100%)	270 (98%)	141 (99%)	
Unknown	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	
Diabetes mellitus							
Number	136	74	139	68	275	142	
Yes	37 (27%)	31 (42%)	43 (31%)	19 (28%)	80 (29%)	50 (35%)	.22
No	99 (73%)	43 (58%)	96 (69%)	49 (72%)	195 (71%)	92 (65%)	
Renal insufficiency							
Number	136	74	139	68	275	142	
Yes	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (0%)	0 (0%)	>.99
No	136 (100%)	74 (100%)	138 (99%)	68 (100%)	274 (100%)	142 (100%)	

Data presented as number (percentage). MC = manual compression.

randomized Vascade subjects and in 56% of MC subjects. The median TTD was 17.2 hours in the Vascade group vs 13.9 hours in the MC group (*P*=.94). Two Dx subjects randomized to Vascade were treated and subsequently referred directly to coronary artery bypass graft (CABG) surgery (an exclusion criteria violation), which resulted in 2 major outliers for TTD (subject 06-230 TTD was 306 hours, subject 07-206 TTD was 432 hours).

Table 3. Study endpoints.

	Diagnostic (n = 211)		Interventional (n = 209)		Total (n = 420)		
	Vascade (n = 137)	MC (n = 74)	Vascade (n = 141)	MC (n = 68)	Vascade (n = 278)	MC (n = 142)	*P*-Value
Efficacy							
TTH (minutes)							
Mean	4.0 ± 4.2	18.2 ± 8.1	5.5 ± 6.3	24.9 ± 15.1	4.8 ± 5.4	21.4 ± 12.4	<.001
Median	2.6 (0.6-24.7)	18.5 (4.3-64.6)	3.3 (0.8-31.6)	20.5 (0.0-97.0)	3.0 (0.6-31.6)	20.0 (0.0-97.0)	<.001
TTA (hours)							
Mean	2.6 ± 2.0	4.6 ± 1.6	5.0 ± 6.7	7.2 ± 3.7	3.8 ± 5.1	5.8 ± 3.1	<.001
Median	2.2 (1.0-20.1)	4.4 (1.7-11.0)	4.1 (2.2-78.0)	6.4 (2.5-22.8)	3.2 (1.0-78.0)	5.2 (1.7-22.8)	<.001
TTDe (hours)							
Mean	3.1 ± 2.1	5.0 ± 1.6	6.6 ± 8.4	8.2 ± 4.0	4.8 ± 6.4	6.5 ± 3.3	<.01
Median	2.6 (1.4-20.5)	4.8 (2.2-11.3)	4.6 (2.6-78.4)	7.0 (3.0-23.2)	3.6 (1.4-78.4)	5.7 (2.2-23.2)	<.001
Access-site related complications							
Major	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	>.99
Minor	2 (1%)	2 (3%)	1 (1%)	8 (12%)	3 (1%)	10 (7%)	<.01

Data presented as mean ± standard deviation, median (range), or number (percentage). MC = manual compression; TTH = time to hemostasis; TTA = time to ambulation; TTDe = time to discharge eligibility.

Per protocol, for the primary effectiveness analysis, a 2-sided *P*<.05 (1-sided *P*<.025) for a favorable Vascade-MC treatment effect in a procedure type adjusted TTH regression analysis constituted the successful demonstration of the Vascade device's overall superiority over MC. With an estimated mean TTH reduction of 16.7 minutes and a 2-sided Wald's *P*<.001, the above criteria were met. For each of the three secondary effectiveness analyses (which included TTH, TTDe, and TTA), the individual 2-sided *P*-value was <.001 and the overall *P*-value was <.001 by simple Bonferroni multiple testing adjustment. Therefore, the protocol-stated success criterion of a 2-sided *P*<.05 for all three secondary effectiveness endpoints combined was met.

The study was designed to capture elapsed time for TTH, TTA, TTDe, and TTD, from the time of device/sheath removal. Per standard of care, the sheath was left in place for MC patients for an average of 28.3 minutes (Dx) and 151.6 minutes (Ix) before removal and application of MC. This translated into additional patient management time that is not reflected in the per-protocol results of the RESPECT study.

No major access-site related complications were reported in either randomized group, and procedure success was achieved in 100% of cases in both arms. Device success was achieved in 263 of the 269 randomized subjects in whom device deployment was attempted per the IFU (98%). Four device-related issues were related to collagen deployment and 2 cases were related to disc deployment.

Minor access-site related complications were significantly reduced (*P*<.01) with Vascade as compared with MC. Minor events were reported in both Vascade subjects (3 events in 3 subjects) and MC subjects (10 events in 10 subjects). Table 4 shows reported events by treatment group and procedure type. In the Vascade group, there was 1 instance of access-site related bleeding requiring >30 minutes to achieve hemostasis (0.4%), access-site related hematoma >6 cm (0.4%) and new-onset access-site related neuropathy in the ipsilateral lower extremity not requiring surgical repair (0.4%) out of 275 subjects (1.1% total) as compared with 10 instances of access-site related bleeding requiring >30 minutes to achieve hemostasis (7%) in the MC group per minor safety endpoint definition. By the Fisher's exact test, the overall proportions of patients reporting any access-site related minor complications, ie, 1.1% Vascade and 7% MC, was significantly different (*P*<.01).

Discussion

This study demonstrates that in comparison with MC, the extravascular Vascade femoral closure device reduces time to hemostasis, time to ambulation, and time to discharge eligibility in both patients undergoing diagnostic angiographic procedures and transcatheter intervention. Furthermore, Vascade significantly reduced minor vascular complications without any difference in major vascular complications. These results were significant in that they were noted in the setting of contemporary anticoagulation strategy employing bivalirudin in the majority of the interventional patients.

VCD usage has been driven by the need for more efficient patient through-put at hospitals and cath labs, reducing the resources required for femoral access management both in the catheterization laboratory and post procedure. The choice of closure method is also driven by the safety profile associated with the closure device, as the clinical impact and cost of femoral access complications are substantial. Resnic et al estimated that the cost attributable to complications can range from approximately $1,400 for a hematoma to more than $5,500 for bleeding events, acute limb ischemia or pseudoaneurysm.[12] Closure methods that accelerate TTH, TTA, and TTD while minimizing major and minor complications will lower overall health-care costs and improve patient care.

Results of the RESPECT trial show similar effectiveness of the Vascade device in terms of reduction in TTH, TTA, and TTDe, as compared with other prospective, randomized and controlled VCD studies,[13-18] but an improvement in safety.[4-11] As a consequence, cost savings and increased patient satisfaction may be recognized with Vascade VCS. The reduced rate of minor access-site related complications of Vascade as compared with MC, with no serious adverse events as experienced in the RESPECT study, is notable.

Study limitations. The primary limitation of this study, as with most studies completed for purposes of obtaining marketing approval, is in patient selection criteria. It should be noted that patients at high risk of femoral artery complications and patients with significant renal insufficiency were excluded from the study. However, cardiologists and interventional radiologists certainly routinely see patients with peripheral vascular disease, bleeding diathesis, renal insufficiency, and morbid obesity. The use of Vascade in some of these higher risk patients could increase complication rates beyond those observed in the RESPECT study. Furthermore, the basis for the greater minor complication rate in the MC group was related to >30 minutes being required to obtain hemostasis in patients undergoing intervention.

Conclusion

The RESPECT trial demonstrates that the extravascular Vascade closure device was safe and effective compared with MC in patients in whom 6 and 7 Fr femoral access was employed in both diagnostic and interventional procedures.

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Table 4. Detailed list of access-site related complications.

	Diagnostic (n = 210)			Interventional (n = 207)			Total (n = 417)		
	Vascade (n = 136)	MC (n = 74)	*P*-Value*	Vascade (n = 139)	MC (n = 68)	*P*-Value*	Vascade (n = 275)	MC (n = 142)	*P*-Value*
Any access-site related minor complication**	2 (1.5%)	2 (2.7%)	.61	1 (0.7%)	8 (11.8%)	<.01	3 (1.1%)	10 (7%)	<.01
Access-site related bleeding requiring >30 minutes to achieve hemostasis (V7)	0 (0%)	2 (2.7%)	.12	1 (0.7%)	8 (11.8%)	<.01	1 (0.4%)	10 (7%)	<.001
Access-site related hematoma >6 cm (V8)	1 (0.7%)	0 (0%)	>.99	0 (0%)	0 (0%)	>.99	1 (0.4%)	0 (0%)	>.99
Late access-site related bleeding (post discharge) (V9)	0 (0%)	0 (0%)	>.99	0 (0%)	0 (0%)	>.99	0 (0%)	0 (0%)	>.99
Ipsilateral lower extremity arterial emboli (V10)	0 (0%)	0 (0%)	>.99	0 (0%)	0 (0%)	>.99	0 (0%)	0 (0%)	>.99
Access-site related vessel laceration (V12)	0 (0%)	0 (0%)	>.99	0 (0%)	0 (0%)	>.99	0 (0%)	0 (0%)	>.99
Access-site wound dehiscence (V13)	0 (0%)	0 (0%)	>.99	0 (0%)	0 (0%)	>.99	0 (0%)	0 (0%)	>.99
Localized access-site infection treated with intramuscular or oral antibiotics (V14)	0 (0%)	0 (0%)	>.99	0 (0%)	0 (0%)	>.99	0 (0%)	0 (0%)	>.99
New-onset access-site related neuropathy in the ipsilateral lower extremity not requiring surgical repair (V18)	1 (0.7%)	0 (0%)	>.99	0 (0%)	0 (0%)	>.99	1 (0.4%)	0 (0%)	>.99
Ipsilateral pedal pulse diminished by two grades or transiently lost (V19)	0 (0%)	0 (0%)	>.99	0 (0%)	0 (0%)	>.99	0 (0%)	0 (0%)	>.99

*Two-sided Fisher's exact test; **Excluding ultrasound substudy to be reported separately. MC = manual compression.

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Funding: Clinical study supported by Cardiva Medical, Inc.

Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Turi reports clinical events committee for Arstasis, Inc and grant from St Jude Medical outside the submitted work. The authors report no conflicts of interest regarding the content herein.

Manuscript submitted May 19, 2014, provisional acceptance given July 1, 2014, final version accepted July 29, 2014.

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COMMENTARY

Where Are We With Vascular Closure Devices After Percutaneous Arteriotomy?

Marc Cohen, MD

"Mind the Gap."
— London subway announcement

In this issue of *the Journal of Invasive Cardiology*, Hermiller and colleagues present the results of their "Pivotal Trial of a Novel Extravascular Collagen-Based Closure Device Compared to Manual Compression in Diagnostic and Interventional Patients: The Vascade VCS RESPECT trial.[1] Previous studies[2-6] established a significant clinical role for suture-based as well as collagen-plug based vascular closure devices (VCDs) in reducing time to hemostasis and ambulation, thereby facilitating early discharge of patients after either diagnostic and/or catheter-based interventions. However, building on these achievements, the RESPECT trial[1] patients treated with the newer Vascade vascular closure system also experienced significantly fewer adverse and minor bleeding events. This is unique within the arena of prior VCD studies.

Objectives of VCDs. The principal objective of any and all devices designed to "close the gap" and seal an arterial puncture site, large or small, is to prevent bleeding from the site. A byproduct of successful sealing of the artery is to then be able to ambulate the patient without fear of leaking around the VCD, and/or to avoid other access-site complications. Interestingly, the currently approved VCDs have been reliably associated with a shorter time to local hemostasis, and ambulation, even with large-bore arteriotomies.[7] However, a small fraction of device deployments fail or are suboptimal, and the objective of significantly fewer bleeding complications after VCD use has not been realized.[8]

Methodology. In attempting to reduce adverse events, the Vascade device, similar to the currently approved Mynx device, achieves hemostasis without leaving any foreign body or material inside the vessel lumen. The Vascade expandable nitinol disk that locates the vessel wall and provides temporary hemostasis is retractable. There are no intravascular components. However, two problems remain with this design that may dilute the benefits if and when Vascade gets approval for clinical use: (1) the disc that locates the vessel wall can get "trapped" by a calcific plaque several millimeters upstream (craniad) from the actual puncture site; and (2) with suture-based devices, hemostasis and device malfunction can be assessed after cinching the sutures with the guidewire still in the vessel lumen, so access is not lost. With the Vascade device, wire access has to be removed in order for the nitinol disk vessel locator to be deployed. Once the disc is retracted, access to the vessel is lost.

Results. Device and procedure success rates with Vascade were 98% and 100%, respectively. Minor adverse events were 1.1% for Vascade and 7% for manual closure (MC). For better or worse, no major access-site related complications were reported in either arm of this trial. This dramatic 5.9% absolute risk reduction in minor complications is the best seen so far with VCDs and sets a new bar for future trials. However, detailed review of the patient cohort in RESPECT generates some concern regarding the reproducibility of these results in a broader catheterization lab population. Would the same reduction in minor adverse events still be observed if unfractionated heparin (UFH) was the routine anticoagulant instead of bivalirudin? Also, it appears that UFH was used for many of the diagnostic cases. Would any superiority with Vascade be observed in labs that do NOT routinely use any anticoagulants for routine, quick, diagnostic cases? The mean body mass index of 30 kg/m^2 in RESPECT could also bias the results. One is left wondering what the deployment success and complication rates would be in the smaller body weight patients who we know are the patients at highest risk for bleeding. Lastly, would the Vascade strategy be equally effective in patients with ST-elevation myocardial infarction, many of whom are still treated with adjunctive intravenous glycoprotein IIb/IIIa therapy?

In the absence of any major bleeding events, is the RESPECT trial just another underpowered clinical trial? Does the absence of evidence allow us to intuit that there is evidence of absence of liability from major bleeding with this device?

Conclusion. Vascade use reduced the rate of minor access site-related complications, and significantly shortened time to hemostasis, ambulation, and eligibility for discharge compared to MC. While there was no formal economic analysis, the RESPECT trial presents us with a win-win proposition in the current medical environment of optimizing resource utilization, and reducing length of stay. Even without data on major bleeding, the impact of reducing minor complications, considering the global use of VCDs[9] would be massive.

Future challenges. Catheterization laboratories in the United States and around the world are becoming more comfortable with adopting alternative access-sites, especially the radial artery approach.[10] Large-bore arteriotomies for transcatheter aortic valve replacement or Impella-supported high-risk percutaneous coronary intervention are now routine worldwide.[7] What will the clinical impact of a 5-7 Fr closure device be 2-3 years from now? Will any trials be conducted to assess the value of VCDs in brachial or axillary artery access sites?[11]

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Disclosure: The author has completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. The author reports no conflicts of interest regarding the content herein.

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