SUMMARY OF SAFETY AND EFFECTIVENESS (SSED)

I. GENERAL INFORMATION

Device Generic Name: Vascular Closure Device

Device Trade Name: VASCADE™ Vascular Closure System (VCS)

Device Product code: MGB

Applicant's Name and Address:

Cardiva Medical, Inc.
888 W. Maude Avenue
Sunnyvale, CA 94085

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P120016

Date of FDA Notice of Approval: January 31, 2013

Expedited: Not applicable

II. INDICATIONS FOR USE

The VASCADE™ Vascular Closure System (VCS) is indicated for femoral arterial access site closure while reducing times to hemostasis and ambulation in patients who have undergone diagnostic or interventional endovascular procedures using a 5F, 6F, or 7F procedural sheath. The VASCADE VCS is also indicated to reduce time to discharge eligibility in patients who have undergone diagnostic endovascular procedures using a 5F, 6F, or 7F procedural sheath.

III. CONTRAINDICATIONS

The VASCADE VCS should not be used in patients with a known allergy to bovine derivatives.

IV. WARNINGS AND PRECAUTIONS

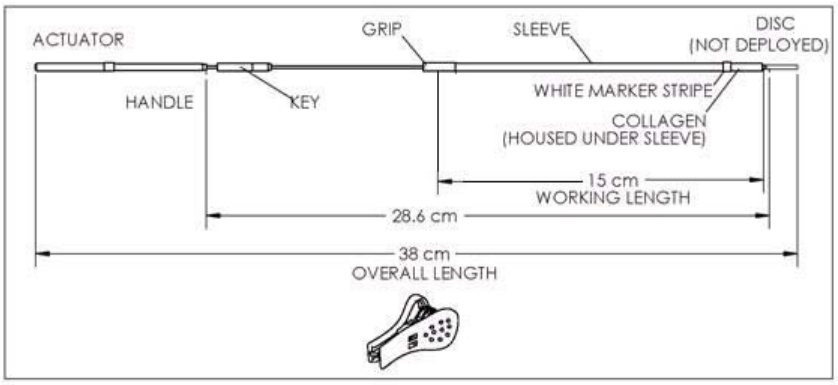
The Warnings and Precautions can be found in the Cardiva VASCADE VCS labeling.

V. DEVICE DESCRIPTION

A. Materials and Configuration

The Cardiva VASCADE family of products consists of a VASCADE 5F VCS and a VASCADE 6/7F VCS. The VASCADE 5F VCS device is used in conjunction with a 5F introducer sheath and the VASCADE 6/7F VCS device is intended for use with either a 6F or 7F sheath. The VASCADE VCS is comprised of a catheter containing a resorbable collagen implant and a clip. The catheter consists of an Actuator assembly, Handle, Key, Grip, Inner and Outer Sleeve Assembly and a NiTi Disc (see Figure 1).

Figure 1. VASCADE VCS (including nominal dimensions)



B. Operation

The VASCADE family of disposable devices is designed to deliver a resorbable collagen patch extravascularly to the arteriotomy site to facilitate hemostasis at the completion of a catheterization procedure. These devices are intended to assist physicians or catheter lab technicians in controlling bleeding from femoral arteriotomy sites and are intended to reduce time to hemostasis, time to ambulation, and time to discharge eligibility. The VASCADE catheter is introduced through the existing sheath at the completion of a catheterization procedure.

To use the system, the catheter is inserted into the artery through the previously placed introducer sheath. After insertion, the distal tip of the catheter is deployed, opening and expanding a low-profile Nitinol (NiTi) disc within the lumen of the artery. The introducer sheath is then removed from the vessel over the catheter and the low-profile disc is placed against the intima, locating the vessel wall and temporarily sealing the arteriotomy. This initial device operation and functionality is, in all essential respects, identical to the Cardiva "Boomerang" and "Catalyst" devices previously cleared via the 510(k) process and successfully used in hundreds of thousands of procedures worldwide.

The position of the device disc against the intima locates the collagen patch in the tissue tract immediately adjacent to the arteriotomy site (extravascularly) and its location is verified using fluoroscopy prior to release. The clip is placed on the device shaft at the surface of the skin to hold the device in place during fluoroscopy. Once the location of the implant has been verified via fluoroscopy, the collagen implant can be released by unlocking its protective sleeve. To unlock the sleeve that covers the implant, a key is slid down the catheter shaft to mate with a lock at the proximal end of the sleeve. Once the sleeve is unlocked, the grip segment of the sleeve assembly is grasped and slid proximally. This action releases the implant in the tissue tract and allows it to hydrate with the surrounding blood in the tissue tract. Moderate tension may be maintained on the device by using the clip during a short (up to 30 second) dwell period to hydrate the implant.

The body's clotting cascade, the arterial wall, and fascia / tissue tract smooth muscle contraction are natural hemostatic responses that provide further wound closure. The hemostatic implant assists in achieving hemostasis by tamponading the puncture site. Once the collagen implant is released, the NiTi disc is collapsed and the catheter is removed. Manual compression may be applied, as desired or necessary, at the site until complete hemostasis (cessation of any oozing) is achieved. The collagen patch is fully resorbed into the body within ~90 days of implantation.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for attaining hemostasis at an arterial puncture site post-catheterization including manual or mechanical compression, percutaneous suture delivery, PEG-based hemostatic devices, collagen plugs with resorbable foot plate, and staples. Pressure dressings and sandbags are routinely used in combination with compression methods to control oozing. The Cardiva Medical Catalyst devices are also used as adjunctive treatment with manual compression. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The VASCADE VCS has been initially marketed on a limited basis in the European Union. The device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of potential adverse effects associated with the use of the device.

- 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, documented by patient symptoms, physical exam, and/or a decreased or absent blood flow on lower extremity angiogram
- 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
- Permanent access site-related nerve injury (> 30 days)
- Access site-related bleeding requiring > 30 minutes to achieve hemostasis
- Access site-related hematoma > 6 cm
- Late access site-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
- Ipsilateral pedal pulse diminished by two grades or transiently lost
- Access site oozing
- Access site bruising
- Access site edema
- Access site inflammation
- Access site pain
- Access site-related vessel intimal tear/dissection
- Access site-related vessel perforation
- Access site-related vasospasm
- Allergic reaction
- Device failure/malfunction

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

A series of *in vitro* tests were conducted to verify the performance of VASCADE. VASCADE devices were tested in accordance with the acceptance criteria defined in the VASCADE product specifications (PS 2793 and PS 2929) or as specified in the design verification test protocols. All of the test results met or exceeded the specified requirements in the product specification and test protocols. A summary of device testing (Table 1) includes, but is not limited to the following:

Table 1: Summary of Device Testing

Purpose	Test	Acceptance Criteria	Results	
			5F	6/7F
Device must be compatible with commercially available introducer sheaths	Overall Device Outer Diameter	6/7F: ≤0.082 inch / 2.083 cm 5F: ≤0.070"	Pass	Pass
	Outer Sleeve Outer Diameter	6/7F: 0.080 ± 0.002 inch 5F: 0.068" ± 0.002"	Pass	Pass
	Tip Outer Diameter at Proximal Sleeve	≤0.065 inch	Pass	Pass
Device should treat patients with greater than 2.5 cm distance from artery to skin surface.	Distance of the collagen implant marker	6/7 F: 2.2 cm ± 0.2 cm 5F: 2.0 cm ± 0.5 cm from the distal side of the proximal sleeve	Pass	Pass
	Implant Length	1.5 ± 0.2 cm	Pass	Pass
Device must be able to reach the arterial access site it intends to seal	Catheter Working Length	15.0 ± 0.5 cm (5.9" ± 0.2")	Pass	Pass
	Catheter Overall Length	38.0 ±1.0 cm (15.0" ± 0.4")	Pass	Pass
Device should be easy to use, simple to deploy, and simple to de-deploy.	Time from device insertion to disc deployment	≤1 minute	Pass	Pass
	Disc deployment force	≤ 2.50 lb	Pass	Pass
	Device de-deployment force	6/7F: ≥ 0.50 lb and ≤ 2.0 lb 5F: ≥ 0.50 lb and ≤ 2.50 lb	Pass	Pass
	The outer sleeve retraction force	Inner Sleeve Retraction Force: ≤ 10 oz Outer Sleeve Retraction Force: ≤ 10 oz	Pass	Pass
Device should maintain position when the disc is deployed in the artery and maintain temporary hemostasis	Clip hold Force	Outer Sleeve: ≥ 1 lb Push Rod: ≥ 1 lb	Pass	Pass
	Deployed Disc Diameter	0.260" ± 0.020" (19F +2/-1F)	Pass	Pass
	Catheter Pull Through Force	> 8 oz	Pass	Pass

Purpose	Test	Acceptance Criteria	Results	
			5F	6/7F
	Multiple Disc Deployment	Device shall be able to withstand deployment and de-deployment at least 5 consecutive times without failure	Pass	Pass
	Prolonged deployment	Sterilized membrane shall be able to withstand deployment for a period of 1 hour.	Pass	Pass
Implant should be fully released within the tissue tract.	Release and swelling of implant	≤ 3 minutes	Pass	Pass
	Collagen Marker Placement and Width	Distance of the collagen implant marker band 2.2 cm ± 0.2 cm Width of collagen marker band 3.5 ± 0.5 mm	Pass	Pass
	Inner Sleeve Slit	Inner sleeve shall have one (1) longitudinal slit.	Pass	Pass
	Outer Sleeve to Inner Sleeve travel limit	0.63 ± 0.05 inch (14.7 – 17.3 mm).	Pass	Pass
Device integrity should be maintained during the procedure.	Joint between pull wire and the inner handle	≥ 3.00 lb (13.34 N)	Pass	Pass
	Joint between the catheter shaft and outer handle	≥ 2.25 lb (10.01 N)	Pass	Pass
	Joint between the back stop and the catheter shaft	≥ 1.30 lb (5.78 N)	Pass	Pass
	Joint between the flared hypotube	≥ 1.30 lb (5.78 N)	Pass	Pass
	Joint between grip and outer sleeve	6/7F: ≥ 3.4 lb (15.12 N) 5F: ≥ 2.25 lb (10.01 N)	Pass	Pass
	Joints constituting the outer sleeve	≥ 1.3 lb (5.78 N)	Pass	Pass
	Joints constituting the inner sleeve	≥ 1.3 lb (5.78 N)	Pass	Pass
	Joints that limit the travel of the outer sleeve over the inner sleeve	≥ 1.3 lb (5.78 N)	Pass	Pass
	Joints constituting the push rod.	≥ 2.25 lb (10.01 N)	Pass	Pass
	Joint between sidewall lumen and tip house	≥ 2.25 lb (10.01N)	Pass	Pass
	Joint between segments for key	≥ 2.25 lb (10.01N)	Pass	Pass
	Joint actuator and the inner handle	≥ 3.00 lb (13.34 N)	Pass	Pass
	Joint between tip of the braid and the pull wire	≥ 3.00 lb (13.34 N)	Pass	Pass
	Proximal braid attachment	≥ 2.25 lb (10.01 N)	Pass	Pass
	Inner handle over-molded joint strength	≥ 3.00 lb (>13.34 N)	Pass	Pass
Implant deployment should be controlled with no risk of inadvertent deployment.	Key Length	6/7F: 1.00±0.100 inch 5F: 1.125”±0.200 inch	Pass	Pass
	Length of Distal Segment of Key (Blue Segment)	6/7F: 0.350 ± 0.050 inch 5F: 0.475± 0.050 inch	Pass	Pass

Purpose	Test	Acceptance Criteria	Results	
			5F	6/7F
	Outer Sleeve lock	No movement at 1.3 lbs or greater in either direction.	Pass	Pass
Implant functionality and position should be maintained until it is ready for deployment.	Collagen displacement post inner sleeve retraction	≤ 2.5mm	Pass	Pass
Device must be able to be seen under fluoroscopy.	Implant material location should be verifiable under fluoroscopy	Proximal Sleeve Length: 0.065 ± 0.003 inch	Pass	Pass
Device must be able to withstand shipping and transportation, and environmental conditioning until it is ready for use	Shipping and Transportation Test	ISO 11607 and ASTM D4169	Pass	Pass
Device packaging must be preserved and be capable of protecting the device until it is ready for use	Packing and Label integrity testing	ISO 11607-1	Pass	Pass
Device must be delivered sterile and non-pyrogenic.	Sterilization	SAL for the catheter and clip: $\geq 10^{-6}$	Pass	Pass
	LAL Testing	Catheter and clip will be ≤20 EU/device.	Pass	Pass
All materials used on the device must be biocompatible	Biocompatibility	Device should be Non-Cytotoxic and comply with ISO 10993	Pass	Pass

Testing of all attribute and functional requirements confirmed that the device as well as its packaging met all product specifications throughout its 2-year shelf-life.

Based on the test results, the VASCADE VCS met the functional, visual, and performance requirements with the pre-determined confidence and reliability. No anomalies were found during testing. The devices met the applicable acceptance criteria prescribed in the test protocol with zero failures.

B. Sterilization

The VASCADE 5F and 6/7F VCS devices are sterilized by gamma radiation in the range of 20-35kGy. The packaging system has been demonstrated to be an appropriate sterile barrier and remains intact throughout device shelf-life. The sterilization process has been validated to deliver a minimum Sterility Assurance Level (SAL) of 10^{-6} for the device and its packaging.

C. Biocompatibility

The VASCADE VCS devices include a delivery catheter as well as an implantable bovine-derived collagen patch. The device was evaluated for biocompatibility in accordance with ISO 10993-1, Biological Evaluation of Medical Devices. The delivery catheter is an "external communicating device" in contact with circulating blood for limited exposure (<24 hours) following arterial catheterization procedures. The collagen patch is classified as an implant device for tissue/bone contact for a permanent duration (>30 days) that has the potential for direct contact with circulating blood.

Delivery Catheter

The biocompatibility testing results, for the delivery catheter, are shown in Table 2.

Table 2. Biocompatibility Summary for VASCADE VCS Delivery Catheter

Test	Test Method – Model	Results
Cytotoxicity Testing	MEM Elution Using L-929 Mouse Fibroblast Cells (ISO) (Cytotoxicity)	Non-Cytotoxic
Sensitization Testing	Guinea Pig Maximum Sensitization Test (ISO)	No evidence of causing delayed dermal contact sensitization
Irritation/Intracutaneous Reactivity Testing	Intracutaneous Irritation Test (ISO)	Non-Irritant
Systemic (Acute) Toxicity Testing	Acute Systemic Injection Test (ISO)	No mortality or evidence of systemic toxicity
Pyrogencity Testing	Material Mediated Rabbit Test (ISO)	Non-Pyrogenic
Hemocompatibility Testing	Complement Activation C3a Assay and SC5b-9 Assay	Able to activate the complement components of the blood
Hemocompatibility Testing	Hemolysis Test (ASTM (F756) Method) Extract / Direct Contact Method	Non-Hemolytic
Partial Thromboplastin Time (PTT)	Partial Thromboplastin Time Essay (PTT)	No evidence of coagulation abnormalities in the intrinsic pathway

The results from the VASCADE VCS delivery catheter biocompatibility testing demonstrated that acceptance criteria for each study were met.

Collagen Patch

The collagen patch is comprised of bovine-dermis derived Type I collagen. Biocompatibility testing for an implant device in permanent contact with tissue/bone was conducted in accordance with the guidelines specified in the FDA Blue Book Memorandum G 95-I and ISO 10993-1. Hemocompatibility testing was performed since the collagen patch has the potential for brief contact with direct circulating blood during device insertion. Table 3 summarizes the biocompatibility tests being performed for the collagen patch.

Table 3: Biocompatibility Summary for the Collagen Patch

Test	Test Method - Model	Results
Cytotoxicity Testing	MEM Elution Using L-929 Mouse Fibroblast Cells (ISO) (Cytotoxicity)	Non-Cytotoxic
Sensitization Testing	Guinea Pig Maximum Sensitization Test (ISO)	No evidence of causing delayed dermal contact sensitization
Irritation/Intracutaneous Reactivity Testing	Intracutaneous Irritation Test (ISO)	Non-Irritant
Systemic (Acute) Toxicity Testing	Acute Systemic Injection Test (ISO)	No mortality or evidence of systemic toxicity
Pyrogencity Testing	Material Mediated Rabbit Test (ISO)	Non-Pyrogenic
Hemocompatibility Testing	Complement Activation C3a Assay and SC5b-9 Assay	Able to activate the complement components of the blood
Hemocompatibility Testing	Hemolysis Test (ASTM (F756) Method) Extract / Direct Contact Method	Non-Hemolytic
Genotoxicology/ Mutagenicity Testing	Bacterial Mutagenicity Test (Ames Assay) Using Four Salmonella Strains and One Escherichia coli	Non-Mutagenic to Salmonellatyphimurium and Escherichia coli
Genotoxicology/ Mutagenicity Testing	In Vitro Mouse Lymphoma Assay-2 Extracts (ISO)	Non-Mutagenic
Partial Thromboplastin Time (PTT)	Partial Thromboplastin Time Essay (PTT)	No evidence of coagulation abnormalities in the intrinsic pathway

The results from the collagen patch biocompatibility testing demonstrate that the acceptance criteria for each study were met and that the processing and sterilization performed by Cardiva to incorporate the collagen patch into the VASCADE VCS did not affect the known biocompatibility of the collagen.

In conclusion, the biocompatibility testing performed on the VASCADE VCS device demonstrated that the requirements of ISO 10993-1 have been met.

D. Animal Studies

A series of acute and chronic animal studies were performed to characterize the safety and effectiveness of the VASCADE VCS device. Both Ovine and Porcine models had previously been identified as appropriate cardiovascular surrogates for the human patient, and they were the primary models used. Studies were conducted to evaluate the functionality of the delivery device as well as the vascular and physiologic responses to the Collagen Patch. The data demonstrate that the Collagen Patch is well tolerated and is resorbed by the body within approximately 90 days as well as device compatibility with the Introducer Sheaths identified in the Instructions for Use.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

Cardiva completed a pivotal clinical study (RESPECT Trial) to establish a reasonable assurance of safety and effectiveness of the VASCADE 6/7F VCS intended for vascular closure following endovascular procedures. This study was a U.S. based study ("RESPECT" Trial) approved under IDE G100246 with one Australian site also participating. Additionally, a small confirmatory study was performed in Australia using the VASCADE 5F VCS. Data from these two clinical studies are the basis for the PMA approval. A summary of these clinical studies is provided below.

A. RESPECT TRIAL Study Design

Patients were treated between September 13, 2011 and June 6, 2012. The database for this PMA reflects data collected through July 2012 and includes all 420 randomized patients (plus 69 roll-in patients). There were 20 U.S. and 1 OUS investigational sites.

The RESPECT Trial was a prospective, multi-center, randomized, open-label, controlled clinical trial designed to evaluate the safety and effectiveness of VASCADE 6/7F VCS in sealing femoral arterial access sites and specifically to facilitate hemostasis, ambulation, eligibility for hospital discharge, and hospital discharge in comparison to manual compression (MC). 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 6F or 7F introducer sheath with up to 12 cm working length. The study was conducted at 20 U.S. institutions and one Australian center.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the RESPECT Trial was limited to adult patients, who were acceptable candidates for an elective, non-emergent diagnostic or interventional endovascular procedure via the common femoral artery using a 6 or 7F introducer sheath. Patients were excluded if they had systemic infection; immunodeficiency; clinically significant peripheral vascular disease; bleeding disorder; ipsilateral femoral arteriotomy within the previous 30 days; previous ipsilateral artery closure using permanent implant-based closure devices; previous vascular grafts or surgery at target access site; planned endovascular procedure within the next 30 days; extreme morbid obesity (BMI greater than 45 kg/m^2) or were underweight (BMI less than 20 kg/m^2); known allergy/adverse reaction to bovine derivatives; planned extended hospitalization; administration of low molecular weight heparin (LMWH) within 8 hours of the procedure; femoral artery diameter less than 6mm at access site; multiple arterial sticks; received unfractionated heparin with an ACT greater than 300 seconds in the absence of a glycoprotein (GP) IIb/IIIa inhibitor or greater than 250 seconds in the presence of a glycoprotein IIb/IIIa inhibitor; intra-procedural bleeding around sheath or suspected intraluminal thrombus, hematoma, pseudoaneurysm, or AV fistula; uncontrolled hypertension; or length of tissue tract estimated to be less than 2.5 cm.

2. Follow-up Schedule

   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 event including bleeding, neurological and other potential device or procedure related adverse effects. One hundred (100) patients underwent a femoral Ultrasound Sub-Study exam.

3. Clinical Endpoints

With regards to safety, the primary safety endpoint was the rate of combined major access site-related complications within 30 ± 7 days following the catheterization procedure. The secondary safety endpoint was the rate of combined minor access site-related complications within 30 ± 7 days following the procedure.

With regards to effectiveness, the primary effectiveness endpoint was time to hemostasis (TTH). The secondary effectiveness endpoints were time to ambulation (TTA), time to discharge eligibility (TTDE), time to hospital discharge (TTD).

With regards to success/failure criteria, procedure success, and device success were evaluated as additional secondary effectiveness measures.

B. **Accountability of PMA Cohort**

At the time of database lock, of 420 patients enrolled in the PMA study, 99% (415) patients were available for analysis at the completion of the study; the 30-day post-operative visit was complete for all available patients.

A total of 420 randomized patients (211 diagnostic patients and 209 interventional patients) and 69 Roll-In patients (consisting of 45 diagnostic patients and 24 interventional patients) were enrolled from September 13, 2011 to June 6, 2012 for a total of 489 patients. Of the randomized diagnostic patients, 137 were assigned to VASCADE and 74 to manual compression. Of the randomized interventional patients, 141 were assigned to VASCADE and 68 to manual compression. A total of 415 randomized patients (99%) completed the final 30-day follow-up assessment. Three (3) patients were prematurely randomized and immediately withdrawn from the study due to final ineligibility; one (1) additional patient was lost to follow-up and 1 patient withdrew consent to participate prior to the 30-day follow-up. A total of 100 consecutive patients were enrolled into an Ultrasound Sub-Study evaluated by a core lab. Reference Table 4 for a summary of patient disposition.

Table 4: Accountability of PMA Cohort

	VASCADE		Manual Compression	
Total Randomized	278		142	
Underwent Endovascular Procedure	275	99%	142	100%
Completed Study	274	99%	141	99%
Early Termination	4	1.4%	1	0.7%
Protocol Deviation	2	0.7%	0	0.0%
Investigator decision	1	0.4%	0	0.0%
Lost to follow-up	0	0.0%	1	0.7%
Withdrew consent to participate in study	1	0.4%	0	0.0%

C. **Study Population Demographics and Baseline Parameters**

The demographics of the study population are typical for a VCS study performed in the US. The baseline demographic and clinical characteristics of the two treatment groups were similar. The mean ages in the VASCADE and manual compression groups were 61.8 ± 11.2 years, and

62.5 ± 10.4 years, respectively. Approximately 29% of the patients in each treatment group were female. Table 5 provides these demographic results.

Table 5: Patient Demographics and Baseline Characteristics – Randomized Patients

	Diagnostic (N=211)				Interventional (N=209)				Total (N=420)					
	VASCADE (N=137)		Manual Compression (N=74)		VASCADE (N=141)		Manual Compression (N=68)		VASCADE (N=278)		Manual Compression (N=142)		p-value	
Age														
N	136		74		139		68		275		142			
Mean	62.2		62.8		61.4		62.3		61.8		62.5		0.51	*
Std Deviation	11.8		11.1		10.6		9.7		11.2		10.4			
Median	64		65		64		63.5		64		64			
Min	30		34		36		40		30		34			
Max	80		79		80		79		80		79			
Gender														
N	136		74		139		68		275		142			
Male	88	65%	47	64%	108	78%	54	79%	196	71%	101	71%		
Female	48	35%	27	36%	31	22%	14	21%	79	29%	41	29%	1.00	**
Ethnicity														
N	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%	0.73	***
Unknown	7	5%	5	7%	2	1%	0	0%	9	3%	5	4%		
Race														
N	136		74		139		68		275		142			
White	120	88%	66	89%	129	93%	64	94%	249	91%	130	92%	0.86	****
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%		
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%		
BMI														
N	136		74		139		68		275		142			
Mean	30.4		30.7		30.1		29.8		30.2		30.2		0.97	*
Std Deviation	4.9		4.9		4.8		5.0		4.8		5.0			
Median	30.3		30.3		29.8		28.8		30.1		29.4			
Min	19.8		21.8		20.7		20.0		19.8		20.0			
Max	44.5		43.8		45.0		41.8		45.0		43.8			
Systolic Blood Pressure														
N	136		74		139		68		275		142			
Mean	134.2		132.5		132.6		133.0		133.4		132.7		0.74	*
Std Deviation	17.9		15.2		18.2		21.2		18.0		18.3			
Median	135		131		130		133		132		131			
Min	97		103		94		96		94		96			
Max	172		175		179		176		179		176			
Diastolic Blood Pressure														
N	136		74		139		68		275		142			
Mean	77.7		76.4		76.7		78.1		77.2		77.2		0.99	*
Std Deviation	10.6		9.8		10.9		11.7		10.7		10.8			
Median	76		76		76		78.5		76		78			
Min	60		59		46		60		46		59			
Max	105		103		110		108		110		108			

* t-test
**Fisher's exact test
***Freeman-Halton exact test
****Fisher's exact test comparing white vs. all other races combined
There were no indication ($p<0.05$) of randomization chance imbalance for any of the above characteristics.

There were no significant differences ($p\geq0.05$) between the treatment and control groups for any of the above characteristics.

Medical History

Medical History and Risk Factors are presented in Table 6. There were also no statistically significant differences ($p \geq 0.05$) between the two treatment groups.

Table 6: Medical History and Risk Factors

	Diagnostic (N=211)				Interventional (N=209)				Total (N=420)				
	VASCADE (N=137)		Manual Compression (N=74)		VASCADE (N=141)		Manual Compression (N=68)		VASCADE (N=278)		Manual Compression (N=142)		p-value
Hypercholesterolemia													
N	136		74		139		68		275		142		
Yes	115	85%	56	76%	118	85%	59	87%	233	85%	115	81%	0.13 *
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													
N	136		74		139		68		275		142		
Yes	102	75%	56	76%	114	82%	53	78%	216	79%	109	77%	0.71 *
No	34	25%	18	24%	25	18%	15	22%	59	21%	33	23%	
Premature Atherosclerotic Disease													
N	136		74		139		68		275		142		
Yes	48	35%	25	34%	78	56%	38	56%	126	46%	63	44%	0.72 *
PVD***	6	4%	1	1%	11	8%	7	10%	17	6%	8	6%	
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													
N	136		74		139		68		275		142		
Yes	58	43%	28	38%	56	40%	30	44%	114	41%	58	41%	0.23 **
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													
N	133		73		138		68		271		141		
Never	60	45%	33	45%	69	50%	24	35%	129	48%	57	40%	0.28 **
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													
N	136		74		139		68		275		142		
Yes	3	2%	0	0%	2	1%	0	0%	5	2%	0	0%	0.09 *
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													
N	136		74		139		68		275		142		
Yes	37	27%	31	42%	43	31%	19	28%	80	29%	50	35%	0.22 *
No	99	73%	43	58%	96	69%	49	72%	195	71%	92	65%	
Renal Insufficiency													
N	136		74		139		68		275		142		
Yes	0	0%	0	0%	1	1%	0	0%	1	0%	0	0%	1.00 *
No	136	100%	74	100%	138	99%	68	100%	274	100%	142	100%	
Neuropathy in Ipsilateral Lower Extremity													
N	136		74		139		68		275		142		
Yes	2	1%	0	0%	2	1%	1	1%	4	1%	1	1%	0.67 *
No	134	99%	74	100%	137	99%	67	99%	271	99%	141	99%	
Other Significant Medical History													
N	136		74		139		68		275		142		
Yes	89	65%	54	73%	82	59%	42	62%	171	62%	96	68%	0.28 *
No	47	35%	20	27%	57	41%	26	38%	104	38%	46	32%	

*Two-sided Fisher's exact test comparing the proportions of Yes vs. No between VASCADE and manual compression totals

**Freeman-Halton exact test comparing the proportions of Yes, No and Unknown between VASCADE and manual compression totals

***Peripheral Vascular Disease: Damage to or dysfunction of the arteries outside the heart resulting in reduced blood flow; especially: narrowing or obstruction (as from atherosclerosis) of an artery (as the iliac artery or femoral artery) supplying the legs that is marked chiefly by intermittent claudication and by numbness and tingling in the legs.

Anti-Coagulant and Antiplatelet Medications

The majority of the enrolled patients (77% of the interventional patients randomized to the VASCADE VCS arm and 69% of the interventional patients randomized to the MC arm) received bivalirudin (Angiomax). Anticoagulant administration including heparin, bivalirudin (Angiomax), and glycoprotein IIb/IIIa inhibitors is shown in Table 7 below.

Table 7: Pre- and Peri-Procedure Anticoagulant/Antiplatelet Medication

	Diagnostic (N=211)				**Interventional (N=209)**				**Total (N=420)**			
Pre-Procedure	**VASCADE (N=137)**		**Manual Compression (N=74)**		**VASCADE (N=141)**		**Manual Compression (N=68)**		**VASCADE (N=278)**		**Manual Compression (N=142)**	
N	136		74		139		68		275		142	
Aspirin	95	70%	54	73%	114	82%	55	81%	209	76%	109	77%
Warfarin	5	4%	4	5%	6	4%	1	1%	11	4%	5	4%
Ticlopidine	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Clopidogrel	31	23%	14	19%	58	42%	20	29%	89	32%	34	24%
Prasugrel	2	1%	1	1%	9	6%	8	12%	11	4%	9	6%
Low molecular weight Heparin	2	1%	4	5%	2	1%	1	1%	4	1%	5	4%
Pradaxa	1	1%	2	3%	1	1%	1	1%	2	1%	3	2%
Aggrenox	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%
Integrilin	0	0%	0	0%	1	1%	0	0%	1	0.4 %	0	0%
Unfractionated Heparin subcutaneous	0	0%	1	1%	0	0%	0	0%	0	0%	1	1%
Any of the above	101	74%	58	78%	123	88%	60	88%	224	81%	118	83%
Peri-Procedure												
N	136		74		139		68		275		142	
Heparin	6	4%	5	7%	37	27%	18	26%	43	16%	23	16%
Bivalirudin	11	8%	3	4%	107	77%	47	69%	118	43%	50	35%
Aspirin	109	80%	56	76%	132	95%	63	93%	241	88%	119	84%
Warfarin	5	4%	3	4%	6	4%	1	1%	11	4%	4	3%
Ticlopidine	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Clopidogeral	33	24%	13	18%	83	60%	40	59%	116	42%	53	37%
Prasugrel	3	2%	1	1%	42	30%	20	29%	45	16%	21	15%
Low molecular weight Heparin	7	5%	1	1%	7	5%	1	1%	14	5%	2	1%
Pradaxa	3	2%	1	1%	1	1%	0	0%	4	1%	1	1%
Brilanta	0	0%	0	0%	9	6%	1	1%	9	3%	1	1%
Heparin Subcutaneous	0	0%	0	0%	1	1%	0	0%	1	0.4 %	0	0%
Aggrenox	0	0%	0	0%	0	0%	1	1%	0	0%	1	1%
Any of the above	114	83%	58	78%	134	95%	64	94%	248	89%	122	86%
Peri-Procedure GP IIB/IIIA Inhibitors												
N	136		74		139		68		275		142	
Integrilin	0	0%	0	0%	9	6%	1	1%	9	3%	1	1%
Aggrastat	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
Reopro	0	0%	0	0%	2	1%	1	1%	2	1%	1	1%
Any of the above	0	0%	0	0%	11	8%	2	3%	11	4%	2	1%

Key Inclusion and Exclusion Criteria are shown in Table 8 below.

Table 8: Inclusion and Exclusion Criteria

Pre-Operative Inclusion Criteria	1. 18 to 80 years of age; 2. Capable and willing to give informed consent; 3. Acceptable candidate for an elective, non-emergent diagnostic or interventional endovascular procedure via the common femoral artery using a 6 Fr or 7 Fr introducer sheath who are also acceptable candidates for post-procedure manual compression; 4. Able and willing to complete a 30 day ± 7 days follow-up evaluation; 5. 100 patients willing to undergo ultrasound prior to discharge; 6. Acceptable candidate for emergent vascular surgery.
Pre-Operative Exclusion Criteria	Patients will be excluded from participating in this trial if they meet any of the following criteria prior to initiation of the endovascular procedure 1. Advanced refusal of blood transfusion, if necessary; 2. Active systemic or cutaneous infection or inflammation; 3. Pre-existing immunodeficiency disorder and/or chronic use of systemic steroids; 4. Known, significant history of bleeding diathesis, coagulopathy, von Willebrand's disease or current platelet count < 100,000 cells/mm3, baseline INR ≥1.8, or fibrinogen level less than 150 mg/dl (if received a fibrinolytic agent within prior 24 hours); 5. Severe co-existing morbidities having a life expectancy of less than 30 days; 6. Currently involved in any other investigational clinical trials; 7. Ipsilateral femoral arteriotomy within the previous 30 days; 8. Planned endovascular procedure within the next 30 days; 9. Previous ipsilateral femoral artery closure using a permanent implant-based closure device; 10. Previous vascular grafts or surgery at the target vessel access site; 11. History of symptomatic peripheral arterial disease, revascularization or deep vein thrombosis in the ipsilateral limb; 12. Unilateral or bilateral lower extremity amputation(s); 13. Significant anemia with a hemoglobin level less than 10 g/dL or a hematocrit less than 30%; 14. Renal insufficiency (serum creatinine of > 2.5 mg/dl); 15. Females who are pregnant, planning to become pregnant within 3 months of the procedure, or lactating; 16. Extreme morbid obesity (BMI greater than 45 kg/m2) or underweight (BMI less than 20 kg/m2); 17. Unable to routinely walk at least 20 feet without assistance (see protocol); 18. Known allergy/adverse reaction to bovine derivatives, sodium hyaluronate or hyaluronan preparations; 19. Procedures that extend hospitalization (e.g., staged endovascular procedure, CABG); 20. Administration of low molecular weight heparin (LMWH) within 8 hours of the procedure.

Intra-Operative Exclusion Criteria:	Patients will be excluded from participating in this trial if any of the following exclusion criteria occur during the endovascular procedure: 1. An introducer sheath with an overall length greater than 11 cm, or not 6 Fr or 7 Fr diameter; 2. Femoral artery diameter less than 6 mm at access site; 3. Difficult insertion of procedural sheath or needle stick problems at the onset of the procedure (e.g., multiple stick attempts, "back wall stick", etc.); 4. Angiographic evidence of more than minimal calcium, atherosclerotic disease, or stent within 1 cm of the puncture site; 5. Overlapping Common Femoral Vein and Femoral Artery at access site; 6. Placement of ipsilateral venous sheath during procedure; 7. Arterial access site located not at common femoral artery (e.g., on or below the bifurcation, above the lower border of the inferior epigastric artery, or above the pelvic brim); 8. More than one access site required; 9. Loss of distal pulses in the ipsilateral extremity during the procedure; 10. Patients receiving unfractionated heparin with an ACT greater than 300 seconds in the absence of a glycoprotein IIb/IIIa inhibitor or greater than 250 seconds in the presence of a glycoprotein IIb/IIIa inhibitor (may wait to remove introducer sheath until ACT level reaches the target value); 11. Intra-procedural bleeding around sheath, or suspected intraluminal thrombus, hematoma, pseudoaneurysm, or AV fistula; 12. Systemic hypertension (BP greater than 180/110 mmHg) or hypotension (BP less than 90/60 mmHg) prior to randomization; 13. Length of the tissue tract, the distance between the anterior arterial wall and skin, is estimated to be less than 2.5 cm; 14. If the physician deems that a different method should be used to achieve hemostasis of the arterial site or that the patient should not attempt ambulation according to the protocol requirements.

D. **Results of RESPECT Trial**

Safety Results from RESPECT Trial

The combined rate of major complications was the primary safety endpoint for the trial. The RESPECT Trial was intended to demonstrate non-inferiority in the rate of major access site-related complications for patients treated with the VASCADE VCS compared to patients treated with manual compression. Table 9 provides an event-based analysis, on an Intent-to-Treat (ITT) basis, of the major access site-related complications reported in the trial for the VASCADE and manual compression patients during the 30-day follow-up period stratified by type of procedure (diagnostic and interventional).

The major complication rate for all patients in the VASCADE group was 0.0% (0/275) compared to 0.0% (0/142) in the manual compression control group. Per protocol, for the primary safety analysis, the VASCADE's access site related major complication rate is considered non-inferior to that of manual compression if the 1-sided 95% confidence upper limit for the VASCADE-MC difference is < 5% in the proportion of patients reporting any major complications. The confidence limit was calculated using a method based on Wilson score confidence intervals for individual proportions (Newcomb, *Statistics in Medicine*, 17, 873-890, 1998). With a major complication rate of 0/275 for VASCADE and 0/142 for manual compression, the 1-sided 95% confidence upper limit for the VASCADE-MC difference is 0.97%, i.e., < 5%. The 99.99% confidence upper limit is 4.79%, which is also < 5%.

Therefore the non-inferiority criterion has been met and the hypothesis of a ≥ 5% increase in VASCADE's major complication rate is strongly rejected (p<0.0001).

Table 9: Access Site-Related Major Complications at 30 Days – Event Based

Access Site-Related Major Complications at 30 Days by Event	Diagnostic (N=210)					Interventional (N=207)					Total (N=417)				
	VASCADE (N=136)		Manual Compression (N=74)		p-value*	VASCADE (N=139)		Manual Compression (N=68)		p-value*	VASCADE (N=275)		Manual Compression (N=142)		p-value*
Any access-site-related major complication	**0**	**0.0%**	**0**	**0.0%**	**1.00**	**0**	**0.0%**	**0**	**0.0%**	**1.00**	**0**	**0.0%**	**0**	**0.0%**	1.00
Access site-related bleeding requiring transfusion	0	0.0%	0	0.0%	1.00	0	0.0%	0	0.0%	1.00	0	0.0%	0	0.0%	1.00
Vascular injury requiring repair	0	0.0%	0	0.0%	1.00	0	0.0%	0	0.0%	1.00	0	0.0%	0	0.0%	1.00
New ipsilateral lower extremity ischemia causing a threat to the viability of the limb	0	0.0%	0	0.0%	1.00	0	0.0%	0	0.0%	1.00	0	0.0%	0	0.0%	1.00
Access site-related infection requiring intravenous antibiotics and/or extended hospitalization	0	0.0%	0	0.0%	1.00	0	0.0%	0	0.0%	1.00	0	0.0%	0	0.0%	1.00
New onset access site-related neuropathy in the ipsilateral lower extremity requiring surgical repair	0	0.0%	0	0.0%	1.00	0	0.0%	0	0.0%	1.00	0	0.0%	0	0.0%	1.00
Permanent access site-related nerve injury (> 30 days)	0	0.0%	0	0.0%	1.00	0	0.0%	0	0.0%	1.00	0	0.0%	0	0.0%	1.00

*Two-sided Fisher's exact test

The combined rate of minor complications was the secondary safety endpoint. Protocol established minor complications are listed in Table 10. The minor complication rate for all patients in the VASCADE group was 1.1% (3/275) compared to 7.0% (10/142) in the manual compression control group. Per protocol, non-inferiority analysis was not performed for access site related minor complications. By the Fisher's exact test, the overall proportions of patients reporting any access site related minor complications, i.e., 1.1% VASCADE and 7.0% manual compression, were statistically significantly different (p=0.002). The primary reason for the difference was more manual compression patients (7%) compared to VASCADE patients (0.4%) reported access site related bleeding requiring > 30 minutes to achieve hemostasis (P=0.0001).

Table 10: Access Site-Related Minor Complications at 30 Days – Event Based

Access Site-Related Minor Complications at 30 Days by Event	Diagnostic (N=210)					Interventional (N=207)					Total (N=417)				
	VASCADE (N=136)		Manual Compression (N=74)		p-value*	VASCADE (N=139)		Manual Compression (N=68)		p-value*	VASCADE (N=275)		Manual Compression (N=142)		p-value*
Any Access Site-Related Minor Complication	**2**	**1.5%**	**2**	**2.7%**	**0.61**	**1**	**0.7%**	**8**	**11.8%**	**0.001**	**3**	**1.1%**	**10**	**7.0%**	**0.002**
Access site-related bleeding requiring > 30 minutes to achieve hemostasis	0	0%	2	2.7%	0.12	1	0.7%	8	11.8%	0.001	1	0.4%	10	7.0%	0.0001
Access site-related hematoma > 6 cm	1	0.7%	0	0%	1.00	0	0%	0	0%	1.00	1	0.4%	0	0%	1.00
Late access site-related bleeding (following hospital discharge)	0	0%	0	0%	1.00	0	0%	0	0%	1.00	0	0%	0	0%	1.00
Ipsilateral lower extremity arterial emboli	0	0%	0	0%	1.00	0	0%	0	0%	1.00	0	0%	0	0%	1.00
Ipsilateral deep vein thrombosis**	3	2.2%	0	0%	NA	1	0.7%	0	0%	NA	4	1.5%	0	0%	NA
Access site-related vessel laceration	0	0%	0	0%	1.00	0	0%	0	0%	1.00	0	0%	0	0%	1.00
Access site wound dehiscence	0	0%	0	0%	1.00	0	0%	0	0%	1.00	0	0%	0	0%	1.00
Localized access site infection treated with intramuscular or oral antibiotics	0	0%	0	0%	1.00	0	0%	0	0%	1.00	0	0%	0	0%	1.00
Arteriovenous fistula not requiring treatment**	0	0%	0	0%	NA	1	0.7%	0	0%	NA	1	0.4%	0	0%	NA
Pseudoaneurysm requiring thrombin injection or fibrin adhesive injection**	0	0%	0	0%	NA	1	0.7%	0	0%	NA	1	0.4%	0	0%	NA
Pseudoaneurysm not requiring treatment**	1	0.7%	0	0%	NA	3	2.2%	0	0%	NA	4	1.5%	0	0%	NA
New onset access site-related neuropathy in the ipsilateral lower extremity not requiring surgical repair	1	0.7%	0	0%	1.00	0	0%	0	0%	1.00	1	0.4%	0	0%	1.00
Ipsilateral pedal pulse diminished by two grades or transiently lost	0	0%	0	0%	1.00	0	0%	0	0%	1.00	0	0%	0	0%	1.00

*Two-sided Fisher's exact test

**Due to different complication-detecting methods between study arms (100 VASCADE patients and no other study patients underwent a femoral ultrasound exam in an ultrasound sub-study), rates for pseudoaneurysm requiring or not requiring treatment, arteriovenous fistula not requiring treatment, and ipsilateral deep vein thrombosis (which were detected by ultrasound exam) are presented but not compared between arms, nor are they included in the computation of the VASCADE overall minor complication rate (top row).

None of the complications in the RESPECT Trial were considered unanticipated events. The observed complication rates support the trial hypotheses that the combined rate of major complications for the VASCADE arm are non-inferior to those of the manual compression control group. There were no deaths during the study.

Effectiveness Results from RESPECT Trial

A total of 417 of the 420 enrolled patients in the RESPECT Trial were evaluable for effectiveness. Results for 210 diagnostic (136 VASCADE and 74 MC) and 207 interventional (139 VASCADE and 68 MC) patients are presented. Times to Hemostasis (TTH), Ambulation (TTA), Discharge Eligibility (TTDE), and Discharge (TTD) are presented in Table 11 below.

The primary efficacy endpoint, TTH, was defined as the elapsed time between device removal, i.e., device removal for Cardiva VASCADE VCS and sheath removal for manual compression, and first observed and confirmed arterial hemostasis (no or minimal subcutaneous oozing and the absence of expanding or developing hematoma). Hemostasis was achieved in significantly less time with the VASCADE VCS device as compared to manual compression. The mean time to hemostasis of 4.8 ± 5.4 minutes (VASCADE) compared with 21.4 ± 12.4 minutes (MC) represents a 16.6 minute reduction in TTH, which is strongly significant ($p<0.0001$).

Table 11: Primary and Secondary Efficacy Endpoints (TTH / TTA / TTDE / TTD)

	Diagnostic (N=211)			Interventional (N=209)			Total (N=420)		
	VASCADE (N=137)	Manual Compression (N=74)	p-value*	VASCADE (N=141)	Manual Compression (N=68)	p-value*	VASCADE (N=278)	Manual Compression (N=142)	p-value*
Time to Hemostasis (minutes)									
N	136	74		139	68		275	142	
Mean	4.0	18.2	< 0.0001	5.5	24.9	< 0.0001	4.8	21.4	< 0.0001
Std Deviation	4.2	8.1		6.3	15.1		5.4	12.4	
Median	2.6	18.5	< 0.0001	3.3	20.5	< 0.0001	3.0	20.0	< 0.0001
Min	0.6	4.3		0.8	0.0		0.6	0.0	
Max	24.7	64.6		31.6	97.0		31.6	97.0	
Time to Ambulation (hours)									
N	136	74		139	68		275	142	
Mean	2.6	4.6	< 0.0001	5.0	7.2	0.003	3.8	5.8	< 0.0001
Std Deviation	2.0	1.6		6.7	3.7		5.1	3.1	
Median	2.2	4.4	< 0.0001	4.1	6.4	< 0.0001	3.2	5.2	< 0.0001
Min	1.0	1.7		2.2	2.5		1.0	1.7	
Max	20.1	11.0		78.0	22.8		78.0	22.8	
Time to Discharge Eligibility (hours)									
N	136	74		138	68		274	142	
Mean	3.1	5.0		6.6	8.2		4.8	6.5	
Std Deviation	2.1	1.6		8.4	4.0		6.4	3.3	
Median	2.6	4.8		4.6	7.0		3.6	5.7	
Min	1.4	2.2		2.6	3.0		1.4	2.2	
Max	20.5	11.3		78.4	23.2		78.4	23.2	
Time to Hospital Discharge (hours)									
N	136	74		139	68		275	142	
Mean	12.0	7.3		24.5	20.8		18.3	13.7	
Std Deviation	45.4	7.3		16.2	6.7		34.5	9.8	
Median	3.4	5.3		23.4	19.9		17.2	13.9	
Min	1.7	2.4		3.4	4.9		1.7	2.4	
Max	432.9	55.6		147.6	45.7		432.9	55.6	

*p-value from t-test for comparing means and Wilcoxon's test for comparing medians

Secondary efficacy endpoints included TTA, TTDE, and TTD. TTA was defined as the elapsed time between device removal, i.e., device removal for Cardiva VASCADE VCS and sheath removal for manual compression, and when ambulation was achieved (patient standing and walking at least 20 feet without re-bleeding). Time to ambulation was significantly

favorable in the VASCADE VCS group as compared with MC with a mean time to ambulation of 3.8 ± 5.1 hours compared with 5.8 ± 3.1 hours in the MC group (2.02 hour difference, p = <0.0001).

TTDE was defined as the elapsed time between device removal, i.e., device removal for Cardiva VASCADE VCS and sheath removal for manual compression, and when the patient was eligible for hospital discharge based upon an assessment of the access site. TTDE was also significantly improved in the VASCADE VCS group with a mean time to discharge eligibility of 4.8 ± 6.4 hours compared with 6.5 ± 3.3 hours in the MC group (1.7 hour difference, p = <0.001).

TTD was defined as the elapsed time between device removal, i.e., device removal for Cardiva VASCADE VCS and sheath removal for manual compression, and when the patient was actually discharged from the hospital. TTD was the only secondary efficacy end-point not found to be favorable to the VASCADE VCS. Mean TTD was 18.3 ± 34.5 hours in the VASCADE VCS group as compared with 13.7 ± 9.8 hours for the MC control. Independent variables such as types of underlying or additional procedures (e.g., CABG surgery) and overall patient condition, having nothing to do with access site closure, have a substantial impact on actual hospital discharge times.

Proportions of patients achieving TTH, TTA, TTDE and TTD at various fixed time points are shown in Table 12, Table 13,

Table 14, and Table 15 for the patients in the RESPECT Trial.

Table 12: Proportions of Patients Achieving Hemostasis at Fixed Time Points

Time point	Diagnostic (N=211)				Interventional (N=209)				Total (N=420)			
	VASCADE (N=137)		Manual Compression (N=74)		VASCADE (N=141)		Manual Compression (N=68)		VASCADE (N=278)		Manual Compression (N=142)	
N	136		74		139		68		275		142	
≤ 1 minute	7	5%	0	0%	1	1%	1	1%	8	3%	1	1%
≤ 2 minutes	30	22%	0	0%	21	15%	1	1%	51	19%	1	1%
≤ 3 minutes	87	64%	0	0%	49	35%	1	1%	136	49%	1	1%
≤ 4 minutes	104	76%	0	0%	91	65%	1	1%	195	71%	1	1%
≤ 5 minutes	112	82%	1	1%	109	78%	4	6%	221	80%	5	4%
≤ 10 minutes	124	91%	9	12%	122	88%	7	10%	246	89%	16	11%
≤ 20 minutes	133	98%	53	72%	130	94%	32	47%	263	96%	85	60%
≤ 30 minutes	136	100%	72	97%	138	99%	60	88%	274	100%	132	93%

Table 13: Proportions of Patients Achieving Ambulation at Fixed Time Points

Time point	Diagnostic (N=211)				Interventional (N=209)				Total (N=420)			
	VASCADE (N=137)		Manual Compression (N=74)		VASCADE (N=141)		Manual Compression (N=68)		VASCADE (N=278)		Manual Compression (N=142)	
N	136		74		139		68		275		142	
≤ 1 hour	0	0%	0	0%	0	0%	0	0%	0	0%	0	0%
≤ 2 hours	22	16%	1	1%	0	0%	0	0%	22	8%	1	1%
≤ 3 hours	117	86%	10	14%	5	4%	2	3%	122	44%	12	8%
≤ 4 hours	123	90%	25	34%	56	40%	6	9%	179	65%	31	22%
≤ 5 hours	132	97%	50	68%	123	88%	18	26%	255	93%	68	48%
≤ 10 hours	134	99%	73	99%	134	96%	58	85%	268	97%	131	92%
≤ 15 hours	135	99%	74	100%	135	97%	64	94%	270	98%	138	97%

Table 14: Proportions of Patients Eligible for Discharge at Fixed Time Points

Time point	Diagnostic (N=211)				Interventional (N=209)				Total (N=420)			
	VASCADE (N=137)		Manual Compression (N=74)		VASCADE (N=141)		Manual Compression (N=68)		VASCADE (N=278)		Manual Compression (N=142)	
N	136		74		138		68		274		142	
≤ 2 hours	10	7%	0	0%	0	0%	0	0%	10	4%	0	0%
≤ 4 hours	117	86%	17	23%	35	25%	3	4%	152	55%	20	14%
≤ 6 hours	132	97%	58	78%	115	83%	21	31%	247	90%	79	56%
≤ 8 hours	132	97%	71	96%	125	91%	46	68%	257	94%	117	82%
≤ 12 hours	134	99%	74	100%	128	93%	57	84%	262	96%	131	92%
≤ 24 hours	136	100%	74	100%	134	97%	68	100%	270	99%	142	100%
≤ 48 hours	136	100%	74	100%	136	99%	68	100%	272	99%	142	100%

Table 15: Proportions of Patients Discharged from Hospital at Fixed Time Points

Time point	Diagnostic (N=211)				Interventional (N=209)				Total (N=420)			
	VASCADE (N=137)		Manual Compression (N=74)		VASCADE (N=141)		Manual Compression (N=68)		VASCADE (N=278)		Manual Compression (N=142)	
N	136		74		139		68		275		142	
≤ 2 hours	1	1%	0	0%	0	0%	0	0%	1	0%	0	0%
≤ 4 hours	84	62%	12	16%	2	1%	0	0%	86	31%	12	8%
≤ 6 hours	112	82%	49	66%	11	8%	1	1%	123	45%	50	35%
≤ 8 hours	117	86%	65	88%	14	10%	1	1%	131	48%	66	46%
≤ 12 hours	119	88%	67	91%	15	11%	2	3%	134	49%	69	49%
≤ 24 hours	125	92%	71	96%	82	59%	58	85%	207	75%	129	91%
≤ 48 hours	131	96%	73	99%	134	96%	68	100%	265	96%	141	99%

Device Success

Device success was defined as 1) Delivery system deployed, 2) collagen delivered, and 3) hemostasis achieved by VASCADE alone or with adjunctive compression. The device success rates for diagnostic and interventional patients are shown in Table 16. Device success for VASCADE treatment was 94% in the Diagnostic arm and 97% in the Interventional arm. The overall device success rate for the total patients was 96%.

Table 16: VASCADE Device Success Rate

Procedure	Number of Patients**	Number of Successes	Success Rate	95% Confidence Interval*	
Diagnostic	136	128	94%	88.7%	97.4%
Interventional	139	135	97%	92.8%	99.2%
Total	**275**	**263**	**96%**	**92.5%**	**97.7%**

*95% Exact Binomial Confidence Interval

**Includes 6 instances of failure to follow written Instructions for Use. Excluding these 6 instances, Device success rates are 96% (Diagnostic), 99% (Interventional) and 98% (Total)

Procedure Success

Procedure success was defined as final hemostasis achieved using any method, with no major vascular complications through 30 days. The procedure success rates are provided in Table 17. The procedure success rate for the VASCADE treatment group was 100% as compared with 100% in the MC group.

Table 17: Proportion of Procedure Success

Procedure	Treatment Assignment	Number of Patients	Number of Successes	Success Rate	95% Confidence Interval*		
Diagnostic	VASCADE	136	136	100%	97%	100%	
	Manual Compression	74	74	100%	95%	100%	
Interventional	VASCADE	139	139	100%	97%	100%	
	Manual Compression	68	68	100%	95%	100%	
Total	Cardiva VCS	275	275	100%	99%	100%	
	Manual Compression	142	142	100%	97%	100%	

*95% Exact Binomial Confidence Interval
**Two-sided Fisher's exact test.

Gender Bias

A higher number of male patients were enrolled in the RESPECT Trial, 71% male versus 29% female, which is a reflection of the general referral pattern for patients undergoing interventional and diagnostic procedures. There was no statistically significant difference in the rate of major or minor complications for either gender. In addition, there was no statistically significant difference in time to hemostasis, ambulation, discharge eligibility or discharge for either gender.

Overall Summary of Safety and Effectiveness Data

The results of the RESPECT Trial successfully met the acceptance criteria for the primary safety and effectiveness endpoints. The results demonstrated non-inferiority in the rates of major complications for patients treated with the VASCADE device compared to patients treated with manual compression. The rate of minor complications for patients treated with the VASCADE device was shown to be less than the rate for patients treated with manual compression. The results from this clinical trial also demonstrated that the time to hemostasis and time to ambulation for patients treated with VASCADE are significantly shorter as compared to patients treated with standard manual compression. In addition, time to discharge eligibility for diagnostic patients treated with VASCADE is significantly shorter as compared to patients treated with standard manual compression. Also, the procedure success rates for patients treated with VASCADE are equivalent to patients treated with standard manual compression.

E. VASCADE 5F Confirmatory Trial

The purpose of the VASCADE 5F study was to confirm the safety and effectiveness of the scaled-down 5F version of the VASCADE 6/7F VCS. The 5F device is virtually identical to the slightly larger 6/7F VCS. The study population was defined as patients undergoing cardiac or peripheral vascular catheterization procedures via the femoral artery approach when using a standard 5F introducer sheath. The study was conducted at a single-center in Australia, and was a prospective, non-randomized, non-blinded, single treatment trial. The inclusion and exclusion

criteria were identical to the U.S. IDE RESPECT Trial with the exception that patients had to be undergoing a catheterization procedure utilizing a 5F introducer sheath.

Thirty (30) patients were enrolled into the study. All of the patients enrolled in the study underwent diagnostic procedures. Patient demographic characteristics at baseline, such as gender, age, and BMI were comparable between the U.S. IDE trial and the 5F Australian confirmatory study. The safety and effectiveness endpoints for the 5F confirmatory study were identical to the 6/7F study. Identical to the pivotal RESPECT trial, the primary safety endpoint was the rate of combined major access site-related complications within 30 ± 7 days following the catheterization procedure. The secondary safety endpoint was the rate of combined minor access site-related complications within 30 ± 7 days following the procedure. Identical to the IDE RESPECT trial, the primary effectiveness endpoint was TTH. The secondary effectiveness endpoints were TTA, TTDE, TTD, procedure success, and device success.

Results of 5F Trial

Safety Results from 5F Trial

There was one site-related major complication resulting in a major access site-related complication rate of 3.3%. One patient had a "high stick" (IE criteria violation and contrary to the Instructions for Use) and reported a retro-peritoneal bleeding requiring transfusion. There were no other major access-site related events (see Table 18).

Table 18: Access Site-Related Major Complications

Access Site-Related Major Complications	**5-French (N=30)**	
Any access-site-related major complication	**1**	**3.3%**
Access site re-bleeding requiring transfusion	1*	3.3%
Vascular injury requiring repair	0	0.0%
New ipsilateral lower extremity ischemia causing a threat to the viability of the limb	0	0.0%
Access site-related infection requiring intravenous antibiotics and/or extended hospitalization	0	0.0%
New onset access site-related neuropathy in the ipsilateral lower extremity requiring surgical repair	0	0.0%
Permanent access site-related nerve injury (> 30 days)	0	0.0%

*One occurrence only.

Similarly, there was only one (1) minor access site-related complication. The overall complication rate was 3.3%. One patient reported a new onset access site-related neuropathy in the ipsilateral lower extremity not requiring surgical repair (see Table 19).

Table 19: Access Site-Related Minor Complications

Access Site-Related Minor Complications	**5-French (N=30)**	
Any Access Site-Related Minor Complication	**1**	**3.3%**
Access site-related bleeding requiring > 30 minutes to achieve hemostasis	0	0.0%
Access site-related hematoma > 6 cm	0	0.0%
Late access site-related bleeding (following hospital discharge)	0	0.0%
Ipsilateral lower extremity arterial emboli	0	0.0%
Ipsilateral deep vein thrombosis	0	0.0%
Access site-related vessel laceration	0	0.0%
Access site wound dehiscence	0	0.0%
Localized access site infection treated with intramuscular or oral antibiotics	0	0.0%
Arteriovenous fistula not requiring treatment	0	0.0%
Pseudoaneurysm requiring thrombin injection or fibrin adhesive injection	0	0.0%
Pseudoaneurysm not requiring treatment	0	0.0%
New onset access site-related neuropathy in the ipsilateral lower extremity not requiring surgical repair	1*	3.3%
Ipsilateral pedal pulse diminished by two grades or transiently lost	0	0.0%

*One occurrence only.

Effectiveness Results from 5F Trial

The primary efficacy endpoint, TTH, was defined in the same way as in the IDE RESPECT trial, as elapsed time between device removal and first observed and confirmed arterial hemostasis (no or minimal subcutaneous oozing and the absence of expanding or developing hematoma). Mean TTH was 3.0 ± 2.4 minutes (see Table 20).

Secondary efficacy endpoints included TTA, TTDE, and TTD. These endpoints were defined in the same way as in the IDE RESPECT trial. TTA, TTDE and TTD results are shown in Table 20. Mean TTA was 4.1 ± 5.9 hours, mean TTDE was 5.6 ± 9.0, and mean TTD was 11.9 ± 16.0. The procedure success rate was 97% and the device success rate was 93%.

Table 20: TTH, TTA, TTDE, and TTD Effectiveness Endpoints

	5 French (N=30)
Time to Hemostasis (minutes)	
N	30
Mean	3.0
Std Deviation	2.4
Median	2.3
Min	0.2
Max	11.8
Time to Ambulation (hours)	.
N	30
Mean	4.1
Std Deviation	5.9
Median	2.3
Min	1.5
Max	25.9
Time to Discharge Eligibility (hours)	.
N	30
Mean	5.6
Std Deviation	9.0
Median	3.1
Min	2.0
Max	46.9
Time to Hospital Discharge (hours)	.
N	30
Mean	11.9
Std Deviation	16.0
Median	3.5
Min	2.0
Max	73.0

Overall Summary of Safety and Effectiveness for 5F Data

The results from the VASCADE 5F clinical trial demonstrate that the major and minor complication rates using the VASCADE 5F VCS device are similar to the rates for the VASCADE 6/7F device. In addition, the time to hemostasis, time to ambulation, and time to discharge eligibility for patients treated with VASCADE 5F VCS are comparable with VASCADE 6/7F VCS. This is as expected given the simple scaled-down nature of the 5F device and the smaller procedural sheath involved with these generally simpler procedures.

Engineering analysis for the scaled down VASCADE 5F VCS included Collagen Patch size calculations resulting in a proportionally smaller Collagen Patch as compared with the VASCADE 6/7F VCS device. These analyses confirmed equivalent tissue tract space-filling capability between the 5F and 6/7F versions of the VASCADE device. In addition, fundamentally the same verification and validation testing was completed for the VASCADE 5F VCS device as was completed for the VASCADE 6/7F VCS device.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint was time to hemostasis. The secondary effectiveness endpoints were time to-ambulation, time to eligibility for hospital discharge, time to actual hospital discharge, procedure success, and device success. The clinical data show that patients treated with the VASCADE VCS had a lower mean time to hemostasis and ambulation than the corresponding times for those patients treated with manual compression, and that the differences in these times are statistically and clinically significant. In addition, diagnostic patients treated with the VASCADE VCS had a lower mean time to discharge eligibility than the corresponding times for those patients treated with manual compression, and the difference in these times is statistically and clinically significant.

B. Safety Conclusions

The adverse effects of the device are based on data collected in clinical studies conducted to support PMA approval as described above. The primary safety endpoint was the combined rate of major complications within 30 ± 7 days following the catheterization procedure. The secondary safety endpoint was the combined rate of minor complications within 30 ± 7 days following the catheterization procedure. There were no major complications in the pivotal study in either arm. Additionally, for the total patients the rate of overall minor complications was statistically significantly less in the VASCADE treatment arm as compared to manual compression.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in a clinical studies conducted to support PMA approval as described above. In summary, the benefits of the VASCADE VCS device include reduced mean TTH (78% reduction), mean TTA (34% reduction), and for diagnostic patients, mean TTDE (38% reduction), as compared with manual compression. Additionally, for the total patients there was a reduced rate of overall minor complications (84% reduction) in the VASCADE VCS device patients as compared to the manual compression patients, but this result must be interpreted with the recognition that minor complications in the VASCADE VCS device patients detected by femoral ultrasound exam in a sub-study, which was not performed in the manual compression patients, were not included in the computation of the VASCADE overall minor complication rate due to non-poolability.

Additional factors that were considered in determining the probable risks and benefits for the VASCADE VCS device included the design of the study, the conduct of the study, the robustness of the analysis of the study results, and the generalizability of the study results. The availability of alternative treatments, patient-centric assessment, and risk mitigation also factored into the overall risk assessment.

In conclusion, given the available information above, the data support that for femoral arterial access site closure in patients who have undergone diagnostic or interventional endovascular procedures, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data provided in PMA Application P120016 support the reasonable assurance of safety and effectiveness of the VASCADE Vascular Closure System when used in accordance with the indications for use in patients who have undergone diagnostic or interventional cardiac or peripheral vascular endovascular procedures utilizing a 5, 6, or 7F procedural sheath. The data support the claims of improved time to hemostasis, time to ambulation in interventional and diagnostic patients, as well as improved time to hospital discharge eligibility in diagnostic patients.

XIII. CDRH DECISION

CDRH issued an approval order on January 31, 2013.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.