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A PROSPECTIVE RANDOMIZED STUDY COMPARING THE TIME TO AMBULATION (TTA) AND SAFETY OF USING A CLOSURE DEVICE ALONE AND IN CONJUNCTION WITH A POTASSIUM FERRATE PAD (STATSEAL ADVANCED) FOLLOWING TRANSCATHER AORTIC VALVE REPLACEMENT (TAVR) VIA THE TRANSFEMORAL ARTERY

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I. INTRODUCTION, BACKGROUND & RATIONALE

Invasive cardiac catheterization-based procedures are done via transradial (TRA) or transfemoral access (TFA). These procedures are important in the diagnosis and treatment of coronary artery disease. Transradial access (TRA) for invasive cardiac catheterization procedures has gained significant popularity around the world compared with the transfemoral access. And in fact, and as early as 2016, the European Society of Cardiology guidelines have given transradial access its highest recommendation (Class I A) over femoral access.[1] The most compelling reason for adopting TRA is the increased patient safety that results from the potential elimination of access site bleeding and vascular complications. In addition, TRA is associated with early sheath removal, improved patient comfort, faster recovery, and lower costs in comparison with transfemoral access.[2-4]

One of the largest concerns of TRA vs TFA, is the occurrence of radial artery occlusion, which is in part related in part to prolonged radial artery compression time with such devices as the trans-radial air-bladder bracelet (TR band [TRB] (Terumo, Tokyo, Japan).[5] Given that safe reduction in compressions times may reduce the risk of radial artery occlusion, we have previously shown that the adjunctive use of a potassium ferrate hemostatic patch (PFHP, Statseal Advanced RAD, Biolife, Sarasota, FL) with a TRB reduces composite overall complications and time to TRB deflation (68±15 vs 138 ± 62 min, P<0.001) as compared to use of the TRB alone.[6,7] The PFHP contains potassium ferrate on a bed of hydrophilic polymer. The polymer rapidly dehydrates and concentrates blood solids, while the potassium ferrate agglomerates the solids & proteins together, forming a seal to the wound to stop bleeding. Beneath the seal, blood solids and proteins continue to concentrate and stack down, promoting hemostasis at the arteriotomy site without components of the PFHP reaching the vessel.

While the TRA provides the ability to perform a broad range of diagnostic and interventional cardiovascular procedures, there are clear limitations to its use. Compared with TRA, transfemoral provides an easier access, less radiation time, and less contrast agent administered to the patient. Importantly, there is still a growing need for TFA in the setting of advancements of structural heart procedures (e.g. use of transcatheter aortic valve replacements) and mechanical circulatory support (e.g. use of left ventricular assist devices such as the Impella). Further, TFA plays an important role on peripheral endovascular interventions such as angioplasty, stenting, atherectomy, and thrombectomy. In these scenarios, TFA cannot be replaced by TRA. Additionally, operators will often times require TFA during the same index or later procedure in the setting of TRA failure due to a variety of reasons including patient discomfort and inability to deliver procedural equipment.

Two of the most common standard of care methods for TFA hemostasis are the suture-mediate closure device Perclose ProGlide™ system (Abbott Vascular, CA, USA) and the collagen-plug mediated Angio-Seal™ (St. Jud Medical) devices. While first generation TFA closure devices were reported to increased vascular complications in comparison to manual compression,[8] closure devices overall have emerged as a safe and effective alternative method to manual compression. Larger registry studies have suggested equivalence of the Perclose™ (Abbott Laboratories) arterial closure device to manual compression, while the Angio-Seal™ (St. Jude Medical) device has shown a decrease in manual compression time following percutaneous coronary intervention (PCI).[9,10] More recently, a separate meta-analysis of randomized trials showed a strong trend for a reduction of major vascular complications with the use of Angio-

Seal™ following PCI,[11] whereas Perclose™ has had equivalent vascular complication compared to manual compression.[12]

The Angio-Seal™ arterial closure device has a bioabsorbable intraluminal anchor and extraluminal collagen plug. More recent iterations of the device now have a 37% greater collagen footprint at the site of arteriotomy. Re-access of the femoral artery is not recommended for at least 3 months in fear of possible embolization of the collagen plug. The Perclose Proglide™ utilizes a monofilament suture, which facilitates knot delivery and helps to retain knot tensile strength. Given, the suture mechanism, TFA at or near the same site is not contraindicated. When comparing these two devices in PCI patients, a recent randomized study showed that while there is no significant difference in major vascular complications between the two devices, time to hemostasis was shorter (5.3 vs. 46.8 min, $P < 0.01$) and time to ambulation was longer (261 vs. 334 min, $P < 0.05$) with the Angio-Seal VIP™ device compared to the Perclose Proglide™.[13]

THE CLINICAL NEED

Despite the use of both the Perclose™ and the Angio-Seal™ commonly for TFA closure there has been no clinically established time to ambulation post-deployment. While time to ambulation varies widely based on operator in both diagnostic and PCI catheterizations (which require anticoagulation), the Perclose™ instructions for use indicate that a patient may ambulate 2 hours after their device is deployed if using a 5-8F sheath[14] and similarly Angio-seal™ recommends ambulation 2 hours after deployment.[15] Particularly for Perclose™, which could otherwise be considered ideal over Angio-Seal™ given its properties allowing for immediate re-access, reducing time to hemostasis and ambulation would be important.[13] To this end, the utility of PFHP would be of particular interest in those undergoing TFA with a Perclose™. While the PFHP have been shown to be safe and decreased time to hemostasis when used in conjunction to manual compression, it has not been studied in conjunction with a closure device.[16] PFHP in conjunction with manual pressure is most commonly used in the catheterization lab when a contraindication to a closure device exists such as severe arterial disease, but may also improve time to hemostasis and ambulation when used in conjunction with a Perclose™. Establishing a safe expedited protocol with use of a closure device and a PFHP could result in multiple favorable clinical and hospital outcomes:

- Decreased femoral artery hemostasis times
- Decreased incidence of oozing, bleeding or hematoma complications
- Facilitate arterial site management to the more specialized catheterization lab staff/personnel that are better trained to recognize complications
- Decreasing time in the cath lab trying to obtain hemostasis, therefore increasing case throughput and number of cases per day
- Decreasing the workload to the staff by virtue of shortened band in place times and improve procedural throughput.
- Facilitate greater patient comfort resulting from decrease supine time and faster wound healing
- Facilitated faster discharge time allowing for more beds to be available during time of critical bed shortages.

Through our pilot study of 180 patients[6] and multicenter randomized clinical trial of 443 TRA patients[7] we were able to show the capabilities of an adjunct PFHP to an additional standard of

care closure device to achieve many of those favorable clinical outcomes. We showed time to complete TRB deflation was 66±14 min with the PFHP vs. 113±56 min for TRB alone (P<0.001) in the setting of no minor rebleeding in the TRB + PFHP group. Furthermore, among PCI patients, time to TRB deflation (68±15 vs 138 ± 62 min, P<0.001) and composite complications [10.0% vs. 24.2%, p=0.04] were reduced with the PFHP.

Thus, the Statseal was demonstrated to facilitate a rapid deflation protocol with the TRB, allowing for in an earlier discharge, without evidence of significantly increased complication of hematomas or radial artery occlusion. The present study is designed to evaluate the use of Statseal in the TFA population in conjunction with use of the Perclose™ TFA closure device.

Additionally, the TFA is the preferred approach for transcatheter aortic valve replacement (TAVR). In contrast to the 6Fr TFA, TAVR procedures require large bore catheters of 14 to 16 Fr in many circumstances. There has been widespread adoption of the Perclose™ TFA closure device, with many institutions, including our own using a single Perclose closure in order to hemostasis. The present study is designed to evaluate the use of Statseal in the TAVR TFA population in conjunction with use of a single Perclose™ TFA closure device.

II. DESCRIPTION OF THE STUDY DEVICE:

A new compound – potassium ferrate, in combination with a hydrophilic polymer which is formed in to a disc when compressed - has been used in conjunction with hemostasis bands to shorten compression times. This product (trade name StatSeal Advanced) is an FDA approved product comprised of a topical hydrophilic polymer and potassium ferrate disc, [Photo 1] formed by compression of the compound.

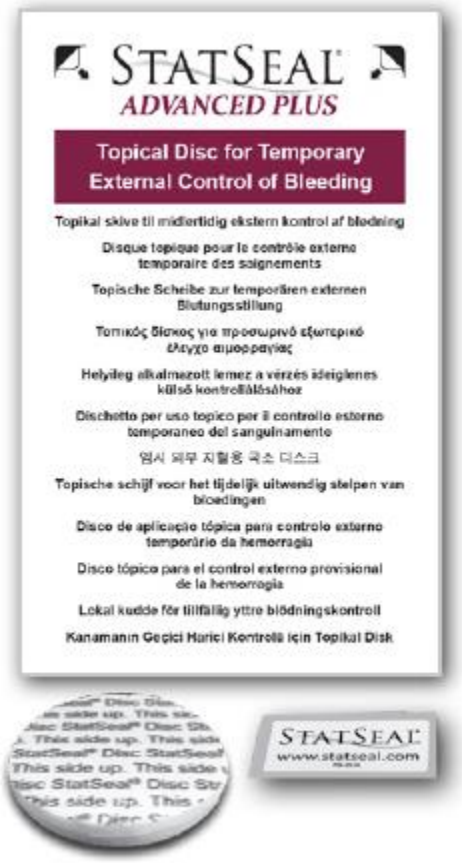

Photo 1: StatSeal Advanced Disc

When in the direct contact with even a small amount of blood, the compound forms an occlusive seal through simultaneous iron-mediated agglomeration of blood solids/proteins and rapid dehydration of the blood. Seal formation is independent of the clotting cascade, facilitating sealing regardless of anticoagulation / antiplatelet status of the patient. Following cessation of pressure being applied to the site, the remnants of StatSeal form what resemble a ‘scab’, and remains in place for 24 hours, covered with a band-aid or Tegaderm patch.

INDICATION FOR USE

StatSeal Advanced is a commercially available product in the United States, and is indicated for use on patients in whom the radial or femoral artery has been used to gain vascular access for a cardiovascular procedure.

DEVICE STORAGE AND ACCOUNTABILITY

StatSeal Advanced is provided in a sterile, foil pouch to protect it from humidity / moisture. As

with most medical products, it should be stored in a cool, dry, secure environment. StatSeal Advance will be provided at no charge by the manufacturer for use in the study.

Damaged devices will be returned to the manufacturer (Biolife, LLC, Sarasota,FL). All unused devices may be retained by the site for continued use, if they so choose.

III. STUDY OBJECTIVE(S)

The primary objectives of this study are to evaluate the performance of StatSeal Advanced used in conjunction with the Perclose™ (SS) as compared to the Perclose™ without SS (PC) relative to:

TAVR Outcomes:

1. Primary outcome: Time to Hemostasis (TTH)
2. Secondary outcome: The incidence of access hematomas

Time to hemostasis (TTH) is defined as the time period required to achieve hemostasis, beginning at the time at which the Perclose™ is depolyed to the access site to when no additional bleeding is appreciated..

Hematoma are defined as being <5 cm, 5-10 cm, and >10 cm. The physician on the study team will make the assessment for the incidence and size of the hematoma based on physical exam and /or diagnostic imaging including ultrasound. Hematoma assessment will be done in multiple incidences: at the time of Perclose deployment while in the catheterization lab, at the time of admission to the recovery unit by the TAVR team, and at the time of admission to the inpatient service for overnight monitoring. While in recovery the patient will be evaluated by the staff for 15 minutes for one hour, every 30 minutes for the next hour, and every hour for the subsequent four hours (for a total of 6 hours post-procedure while in the recovery unit).While admitted for overnight monitoring (at least for a 24 hour period), the patient will have their site evaluated every 4 hours until the 24 hours period has been reached.

IV. STUDY DESIGN AND METHODOLOGY

STUDY DESIGN

This study is a physician initiated, prospective, observational, two arm, randomized study to be performed at one academically affiliated with high catheterization volumes. Enrollment with continue at each site on discretion of the investigators until at least 50 patients are enrolled Clinicians will perform the catheterization in accordance with local standard practice, with no minimum amount of anticoagulation required during the procedure.

STUDY METHODS;

Patient Selection Criteria Study subjects will be identified in their outpatient appointments during their appointments with the structural heart team prior to their TAVR procedure.

Inclusion Criteria:

- Left heart catheterization with plans for delivery of a 14-16 Fr TAVR system

Exclusion Criteria:

Candidates for this study will be excluded if any **one** of the following criteria is true.

- Use of a hemostasis method or device besides Perclose™ (Perclose may not be used in situations of heavy calcification, presence of dissection, etc).
- Use of an anticoagulant other than unfractionated heparin or bivalirudin during the procedure.
- Any use of glycoprotein inhibitors or cangrelor.
- Use of sheathless guides.
- Any anticipated need for continued anticoagulation post-catheterization, including extended bivalirudin infusion.
- Any active treatment with oral anticoagulants continued during course of procedure.
- Presence of arteriovenous dialysis fistula in the ipsilateral leg.
- Any physical deformity or trauma / injury of the leg that would prevent proper placement or function of the hemostasis band.
- Inability of the patient to personally consent for the study. (no surrogate consent)
- Cardiogenic shock, emergent procedures (high risk myocardial infarctions), or any clinical instability as assessed by the physician performing the procedure.

Transfemoral Catheterization Procedure

TFA Cardiac Catheterization will be performed according to local practice standards with use of a 14-16 Fr sheath during a TAVR procedure.

Patients will have their activated clotting time measured prior to sheath removal and at least 5 minutes following the initial dose of anticoagulant. Additional activated clotting time measurements for PCI would be expected as part of routine practice but not recorded. Vasodilators (nitroglycerin, verapamil) will be administered in accordance with local practice.

Timing of Subject Enrollment

A subject will be consented into the study prior to the administration of sedation prior to the procedure, and randomized at the conclusion of a successful deployment of the Perclose device (after all anticoagulation and antiplatelet medication decisions have been made), at which time placement of the assigned device will occur. Eligibility for the study will be assessed at this time and the subject will have to meet all of the inclusion criteria and none of the exclusion criteria.

Randomization will be performed by means of sealed envelopes in randomization blocks of 25. Each envelope will be labeled by patient number containing device designation. Device designation in the envelopes will be random in occurrence. When a patient is officially enrolled (after Perclose™ deployment) the envelope corresponding to that patient number in the Study Patient log will be pulled, opened, and the assignment revealed.

End of Study Status / Effect of Withdrawals:

A subject will have completed the study when one of the following events is documented:

1. The patient is successfully enrolled, treated with a Perclose™, and completes all required follow up.

2. A subject withdraws consent to participate. Patients who withdraw from the study will have their data included to the extent allowable by law. As all study related procedures are expected to be completed on the day of the procedure or day after, subject withdrawal is not considered likely.

Protocol:

Informed Consent:
Subjects must have read the contents of the written informed consent document, had all questions regarding the study adequately answered by study staff, and signed and dated the document prior to any study related activities.

14/16 (TAVR) French Control patients: Patients will have a Perclose™ device deployed at the arteriotomy. Manual pressure will be held for at least 5 minutes, the beginning of which will correspond to time point zero. Patent hemostasis will be documented after device deployment. Any manual compression needed or per protocol under the disgression of the operator will count towards the time to hemostasis. After hemostasis is achieved in the cath lab the patient will be sent to the post-operative area and monitored for further bleeding or hematoma formation as described previously.

14/16 (TAVR) French Statseal Protocol: Patients will have a Perclose™ device deployed at the arteriotomy. A Statseal Advance (SS) disc will applied with 2 piece of gauge over it and manual pressure will be held for at least 5 minute, the beginning of which will correspond to time point zero Patent hemostasis will be documented after device deployment. Any manual compression needed or per protocol under the disgression of the operator will count towards the time to hemostasis. After hemostasis is achieved in the cath lab, the patient will be sent to the post-operative area and monitored for further bleeding or hematoma formation as described previously.

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STUDY OVERVIEW GRAPHIC

V. STUDY DEFINITIONS AND OUTCOMES

Definitions of Baseline and Procedural Variables:

Smoking: Active smoking or >20 pack year tobacco history.

Diabetes: Hgb A1C >6.5% or active medical treatment for diabetes.

Hypercholesterolemia: LDL >130 or on treatment with antilipemic agents.

Hypertension: >140/80 or on medical treatment for hypertension.

Diagnostic procedure: Involving diagnostic catheters only.

Interventional procedure: Involving an interventional wire and therapeutic ACT typically >200, including for fractional flow reserve measurement where a stent is not placed.

Puncture attempts: Number of forward advances of the needle (not puncture sites) needed to achieve access

Procedure Start Time: Time when lidocaine is administered, prior to first puncture attempt.

Procedure End Time: Time when sheath is removed

Primary Efficacy Outcome:

- Total Time to Hemostasis (TTH), defined as from the time of manual compression after Perclose™ deployed until no further bleeding..

Primary Safety Outcome:

- Hematoma formation: small ranging from small <5cm [I], 5-10cm [II] , or large >10cm. Hematoma assessment will be done in multiple incidences: at the time of Perclose deployment while in the catheterization lab, at the time of admission to the recovery unit by the TAVR team, and at the time of admission to the inpatient service for overnight monitoring. While in recovery the patient will be evaluated by the staff for 15 minutes for one hour, every 30 minutes for the next hour, and every hour for the subsequent four hours (for a total of 6 hours post-procedure while in the recovery unit).While admitted for overnight monitoring (at least for a 24 hour period), the patient will have their site evaluated every 4 hours until the 24 hours period has been reached.

VI. STUDY STATISTICAL PLAN:

This is a physician initiated, prospective, randomized, two-arm study, to be conducted at high-

volume academically affiliated centers with the cath lab staff having a (minimum) ten case experience using StatSeal Advanced. The primary analysis will be by intention-to-treat methodology.

A sample size of 50 patients is sufficient to have >90% power to detect an average expected difference of 10 minutes in time (5 min vs 15 min) to hemostasis (different primary outcomes compared to 6F study) between the SS and Perclose groups, using a two-sided alpha of 0.05. A standard deviation of 10 minutes is assumed, which will be the additional time for manual compression if any site ozzing/bleeding is seen after the initial compression. A different standard deviation time was assumed given larger bore access for TAVR TFA acess.

Descriptive summary statistics will be presented for all study variables. Continuous variables will be displayed as means with standard deviations and medians with 75th and 25th percentiles. Categorical variables will be summarized as frequencies with their respective percentages with two-sided 95% exact confidence intervals of the percentages. Statistical comparisons for continuous variables will be performed using the Student's t test or Mann-Whitney U test, as appropriate. Comparisons for categorical variables will be performed using the Chi square test or Fisher exact test, as appropriate. A two-sided P value of 0.05 will be considered statistically significant.

A single multivariate logistic regression will be reported for the safety outcome of hematoma formation. In order to create this model, study arm and variables known to place patients at higher risk for hematoma formation will tested in univariate analysis for the primary safety outcome. Those variables with a P<0.10 will be included in backwards stepwise regression modeling to obtain a final model. Similar to our prior published study,[17] the following variables will be analyzed: Age, sex, weight, hypertension, diabetes, creatinine, pre-procedural INR, pre-procedural platelet level, heparin dose given, PCI, last ACT prior to procedural end, and last SBP prior to procedural end.

VII. ADVERSE EVENTS:

Reports of all adverse events will be made and recorded for the duration of the study, and categorized as specific to those complications associated with femoral access, such as hematoma, bleeding, and other vascular access complications. Those complications not related to vascular access will be stored locally only.

Adverse events will be recorded on the case report forms (CRF) and adjudicated by the site Principal Investigator as to their severity and whether or not directly, indirectly, or not connected to the study devices, and forwarded to the Data Center for entry in to the database.

Adverse Event

Any clinically relevant event that occurs during the performance of the study that puts the subject at additional risk of injury, whether foreseen or not, and requires additional care beyond that expected as a result of the study.

Adverse Device Event

An adverse event related to the use of the device. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, or operation, or any malfunction of

the device. This definition also includes any event resulting from user error or from intentional misuse of the device by the investigator.

Serious Adverse Event

A serious adverse event (SAE) is defined as an adverse event that:

- Led to death,
- Led to a serious deterioration in health that either,
    - Resulted in a life-threatening illness or injury, or
    - Resulted in a permanent impairment of a body structure or a body function, or
    - Required in-patient hospitalization, or
    - Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.

    Note: This includes device deficiencies that might have led to a serious adverse event if (a) suitable action had not been taken or (b) intervention had not been made or (c) if circumstances had been less fortunate.

VIII. DATA MANAGEMENT

Data Collection Process

Data will be collected in an anonymized (coded) fashion using case report forms for each subject. CRFs will be transmitted to the data center for entry in to the database. Data may be collected by clinical research personnel assigned to the study, under the supervision of the investigator.

Data Confidentiality

Subject data will be collected in an anonymous form. Each site will keep a confidential, site – only log of enrolled patients connecting their identity to a coded subject identifier. Each subject will be entered on the log along with procedure date and will be assigned a patient study number comprised of the site number and sequential subject number enrolled. This coded number will be used in the CRFs. For example, John Q Doe, the 12th patient enrolled at site number 2, will be assigned study identifier 002-012. All activities will be performed in compliance with HIPPAA and Good Clinical Practice standards

Data Center

CRFs or coded anonymized data will be forwarded to the Central Data Center, checked for completeness, and entered in the Database as received. Incomplete forms will be returned to the study site for completion. Electronic submission of Data may be employed, but is not required.

See the “Study Statistical Plan” for a description of the plan.

IX. ETHICAL, REGULATORY & ADMINISTRATIVE REQUIREMENTS

The devices being studied in this clinical plan, and the tests performed under it, are approved for marketing by the US-FDA for use as described and have been in use for cardiac catheterization procedures at the participating institutions. FDA approval of the study is not required. No part of the study uses any device or test that is considered investigational.

Investigational Review Board Approvals.
Data from this study may be used for publication in the scientific literature, and therefor IRB approval is required. No patient may be enrolled until IRB approval is granted, and an Informed Consent approved by the IRB is signed by the subject.

Protocol Adherence and Amendments
Investigators will be required to adhere to the protocol requirements. Deviations or violations of the protocol may result in dismissal from the study.

Informed Consent
Each subject in the study must sign the informed consent agreeing to participation.

Alternatives to Participation

As a voluntary randomized study, the patient's alternative to participation is primarily to the local standard of care, typically involving the Perclose alone or Perclose with manual compression, used per local protocol. SS devices may be used outside of the study depending on local practice and availability.

Enrollment in other studies

Simultaneous or dual enrollment in other investigative or observational protocols that do not involve vascular access, anticoagulation, or antiplatelet agents is expressly permitted. The interventions in this trial are not expected to significantly impact upon the outcomes of other protocols, however, the site investigator is responsible for ensuring that there is no conflict with dual enrollment from the standpoint of the other trial.

Study Activities
The Investigator is required to perform the study in accordance with the protocol and to use devices per their instructions for use.

Follow-Up
There is no requirement for the subjects taking part in the study to be seen or examined for any follow up relative to the study following completion of activities described herein.

CRFs
CRFs will be completed for each subject. See Appendix 1 for the CRFs.

Records and Retention
Copies of all records will be retained by the investigator at each site for 2 years.

(Model) Patient Informed Consent
See Appendix 2

Communication with the Principal Investigator:
All communication regarding the study should be routed directly to the Principal Investigator. Copies of all correspondence regarding the study should be maintained in the Site Investigator study file.

Declaration of Helsinki & HIPPAA
The Principal Investigator will ensure that this study is performed in conformity with the Declaration of Helsinki, HIPPAA, and all local and national regulations.

Investigator Responsibilities

- Adhere to all of the required elements of the Clinical Protocol
- Resolve queries in a timely manner
- Participate in Investigator meetings and emails, if scheduled
- Comply with the Declaration of Helsinki
- Obtain written Informed Consent from each study participant before any study specific procedures are performed
- Complete all required case report forms (CRFs) for each subject
- Comply with all applicable regulations and codes of approvals from the site IRB and other Regulatory Authorities
- Notify the Principal Investigator of personnel changes that may affect the study protocol
- Retain all records and study files as required, after which the files may be destroyed.
- Allow direct access to source data/documents, including patient records, in case of monitoring, auditing and/or inspection by the IRB and/or other regulatory authority bodies.

X. RISK BENEFIT ANALYSIS

General Risks and Presumed Benefits:
Application of a hemostatic device in a setting absent an actual femoral arteriotomy presents negligible risk to the subject.

Patients assigned to the SS group may enjoy less discomfort from the shorter length of time needed to lay flat as compared to the Perclose being placed by itself, presuming that the SS does reduce the time to ambulation.

The potential benefit of subject participation is gratification from making a contribution to science helping to demonstrate the effectiveness of a new clinical method to achieve hemostasis following a femoral artery procedure. This new method could potentially provide a safer, more efficient, and more effective hemostatic device for clinicians to use in treating patients undergoing the femoral artery approach for cardiovascular procedures.

Risks related to Perclose Device:
Currently marketed Perclose devices have been associated with complications such as, but not limited to, skin irritation, femoral artery or branch occlusion, arterial dissection, hematoma, pseudoaneurysm, failure to achieve hemostasis, and general groin discomfort.

Risks Specific to the Study Device:
There are no known risks specific to the study device.

Risk Mitigation:
Every effort will be made to mitigate risks in this Study. Those efforts include requiring investigators to be highly experienced operators.

Clinical monitoring will occur in real time to ensure the accurate collection and reporting of data, and ensure that the Site is in compliance with the clinical protocol requirements that mitigate risk

such as patient entry criteria, use of the study device in accordance with instructions, and compliance with study test procedures and methods.

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APPENDICES:

Appendix 1: Sample Patient information sheet

Appendix 2: CRF's