SAINT LUKE'S HOSPITAL

RESEARCH PROTOCOL INVOLVING HUMAN SUBJECTS

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Principal Investigator: Sanjaya Gupta, MD

Study Title: VAscular Closure for Cardiac Ablation Registry (VACCAR)

Co- Investigator(s): Rakesh Ponnapureddy, MD

I. Purpose, Background and Rationale

A. Aim and Hypotheses

Vascular Closure Devices (VCD) have been used to achieve hemostasis of arterial access sites following cardiac catheterization procedures. There is extensive literature available supporting the use of these devices for arterial access site closure, showing reduced time to hemostasis, earlier ambulation and reduced length of hospital stay in comparison to manual compression which is the traditional approach to achieve access site hemostasis. In contrast, there is not significant evidence supporting the use of these devices for closure of femoral venous access site, partly due to limited use of VCD in cardiac electrophysiology procedures, such as catheter ablation for atrial fibrillation and atrial flutter. Another alternative to manual compression, the Figure of 8 stitch has also been used to achieve vascular closure follow catheter ablation of atrial fibrillation and atrial flutter, however it has not been studied formally.

The aim of this registry is to better understand the 'real-world' utilization of VCD or Figure of 8 stitch(F08S) in cardiac ablation procedures and to understand any potential difference between VCD or F08S and manual compression. The outcomes of interest are vascular access site complication rate, time to ambulation and patient perception of pain and overall satisfaction, which is assessed via a survey. The hypothesis of this registry is that there will be an increased patient satisfaction and decreased rate of vascular and bleeding complications with use of either Perclose Proglide system or Figure of 8 stitch for venous closure post atrial fibrillation ablation and atrial flutter ablation procedures in comparison to standard manual compression**.**

B. Background and Significance

Vascular access site complications are an important cause of morbidity following cardiac catheterization procedures. These include recurrent access site bleeding, hematoma

formation, pseudoaneurysm, arterio-venous fistula, acute vascular thrombosis and distal embolization. Manual compression (MC) for 15- 30 minutes has been the 'gold standard' in achieving hemostasis of the access site after these procedures. However, this approach is limited by the need for transient interruption of heparin anticoagulation to perform sheath removal, prolonged bed rest of several hours post sheath removal, patient discomfort, and increased time demand for health care providers to perform manual closure. Vascular Closure Devices (VCD) were introduced into clinical practice in the mid-1990s with the aim of reducing access site bleeding associated with percutaneous coronary intervention procedures. [1]

Several trials, involving patients who had arterial access, have demonstrated increased efficacy of VCD in comparison to MC as evidenced by a reduced time to hemostasis, earlier ambulation and reduced length of hospital stay. However, there are two studies that demonstrated an increased risk of vascular complications associated with use of these vascular closure devices, in particular groin hematoma and arterial pseudoaneurysm.[2,3] A larger meta-analysis that included 30 studies involving 37,066 patients concluded that the risk of complications was dependent upon the specific vascular closure device used and whether the procedure was a diagnostic catheterization or a percutaneous coronary intervention. In the overall analysis, these studies demonstrate a 2.25 fold increase in risk of complications with a VCD.[4]

Despite this finding, the size of each of these individual trials included in the meta-analysis was modest (100-500 patients) and these studies were not powered for safety end points such as access site bleeding and pseudoanerysm. Hence, it is difficult to draw conclusions about safety end points from this meta-analysis. To address this issue, recently, a large multicenter randomized controlled trial (RCT) compared VCD to MC and concluded that VCD was non-inferior in terms of vascular access site complications and was associated with reduced time to hemostasis.[5,6]

There have been only a few studies assessing patient comfort and satisfaction with VCD. A RCT showed VCD to be associated with greater patient satisfaction compared to compression. It also allowed for earlier hemostasis and ambulation compared with both compression and VCD. [9] A study comparing one brand of VCD with compression showed significantly increased patient comfort, assessed by visual analogue scales, with VCD use. [10] A prospective study involving 1500 patients undergoing PCI procedures, followed by access site closure with MC, or two brands of VCD showed that patients treated with 1 brand (Angio- Seal) reported greater overall satisfaction, better wound healing and lower discomfort in comparison to the other brand of VCD (Perclose Proglide) and MC.[11] Overall, the increase in patient satisfaction and decreased time to hemostasis with VCD use,

with no significant increase in complications provided a sound rationale for use of VCD over MC in daily clinical practice for arterial closure.

In contrast to the arterial access studies summarized above, only a few small scale studies assessing the use of VCD for femoral venous access closure site have been published. A retrospective analysis of 26 patients undergoing deployment of VCD following cardiac electrophysiology procedures, published in 2015, showed successful deployment of 75 out of 76 vascular closure devices and they were no complications reported. [7] Another study involving 761 VCD deployments in the femoral vein following catheter ablation for atrial fibrillation procedure showed no significant reduction in vascular or non-vascular bleeding rate in comparison to MC. [8]

Catheter ablation for treatment of atrial fibrillation/atrial flutter is a commonly performed procedure involving placement of 3 or 4 large (8-14 French) sheaths in the femoral vein. The procedure is performed on uninterrupted anticoagulation, which indicates that for warfarin and rivaroxaban the procedure is performed without holding any doses of anticoagulant medication. For apixaban, dabigatran and edoxaban, the procedure is performed with holding the dose of anticoagulant the night before the procedure and the morning of the procedure. The current standard of care is that at the conclusion of atrial fibrillation or atrial flutter ablation procedure, all venous sheaths are kept in place and the patient is transported to a recovery unit. Upon arrival in the recovery unit, the nursing staff will assess the ACT. Sheaths are not removed via manual compression until the ACT is < 165 seconds. During this time period, which may take several hours, the patients are lying flat on their back with their legs straight. Once the ACT is <165 seconds, the nurses will apply manual compression for 15 to 20 minutes. Following hemostasis, the patients lie flat with their legs straight for 3-4 hours. At that point, the access sites are rechecked to ensure hemostasis, and then the patient is allowed to ambulate.

In contrast, the patient receiving a vascular closure device (VCD) undergoes sheath removal at the conclusion of the procedure and hemostasis is achieved before the patient is removed from the table. When the patient is transported to recovery, they must lie flat on their back for 1 hour and then they are permitted to ambulate, irrespective of their ACT. Both patients receiving MC and VCD are monitored overnight for any post op complications such as recurrent bleeding, hematoma, pain or swelling from vascular access site.

Similarly, the Figure of 8 stitch has been used to achieve vascular closure following procedures involved access to the femoral vein, including leadless pacemaker implantation as well as catheter ablation of atrial fibrillation and atrial flutter. The process involves placing 0 silk suture through the skin and subcutaneous tissue below the lowest venous

access site and then through the skin and subcutaneous tissue above the highest venous access site in a Figure of 8 pattern. The Figure of 8 stitch requires administration of protamine a few minutes prior to sheath removal, removing the sheaths and the tying the 0 silk suture which pulls together the skin and tissue above and below the access site and then holding pressure at the groin for 5 minutes after application of the F08S. The following day, the F08S has to be cut prior to discharge. In a study of 200 patients undergoing cryoablation, patients were allocated to receive manual compression or F08S. There was no significant difference in incidence of hematoma or re-bleeding at the access site between the two groups [12] .

It is not known if routine use of VCD or F08S would lead to increased patient satisfaction, earlier ambulation, earlier discharge and decreased rate of complications.

This registry is Investigator initiated.

C. Rationale

The rationale of this registry is to better understand the 'real-world' utilization of VCD and F08S in cardiac ablation procedures and to understand any potential difference between VCD/ F08S and manual compression. The outcomes of interest are vascular access site complication rate, time to ambulation and patient perception of pain and overall satisfaction, which is assessed via a survey.
The aim of this registry to assess difference in patient satisfaction and rate of vascular and bleeding complications with use of either Perclose Proglide system or F08S for venous closure post atrial fibrillation ablation and atrial flutter ablation procedures in comparison to standard manual compression. If they are found to increase patient satisfaction as hypothesized, cardiac electrophysiologists can use VCD or F08S for access site closure instead of manual compression.

II. Research Plan and Design

A. Study Objectives: The objective of this registry is to find out if there is a difference in patient satisfaction and rate of vascular and bleeding complications with use of Perclose Proglide system or F08S for venous closure post atrial fibrillation and atrial flutter procedures in comparison to manual compression.

B. Study Type and Design: The design will be a prospective observational registry collecting data on patients who underwent catheter ablation for atrial fibrillation and atrial flutter, including administration of a patient survey.

C. Sample size, statistical methods, and power calculation

As a registry, there is no targeted enrollment, however it is expected that approximately 120 patients would be enrolled in 6 months.

D. Subject Criteria (See Vulnerable Populations appendix, if applicable):

1. Inclusion criteria:

- Patients undergoing a catheter ablation procedure (radiofrequency ablation or cryoablation) to treat symptomatic paroxysmal atrial fibrillation or atrial flutter.
- Patients willing to participate in a short written survey.

2. Exclusion criteria:

- Patients undergoing ablation for an arrhythmia other than atrial fibrillation/atrial flutter or who are not candidates for an ablation procedure for treatment of atrial fibrillation/atrial flutter.
- Patients who are not able to read or understand the English language.
- Patients who had recent access site complications within the same hospitalization.
- Patients who have baseline thrombocytopenia (platelet count less than 80) or known coagulopathy (INR > 1.5).

3. Withdrawal/Termination criteria:

No necessary safety precautions are to be applied to those who withdraw.
A study subject may participate in any another research study while participating in this registry.

E. Specific methods and techniques used throughout the study

Once approval from the Institutional Review Board is obtained, patients who underwent catheter ablation for atrial fibrillation or atrial flutter will be approached for inclusion in this registry. The morning after the procedure, patients will be requested to fill out informed consent documents, followed by a survey (Appendix A). This survey will include parameters such as their perception of pain following the procedure, discomfort experienced, any complications that may have occurred after the procedure, their preference if a repeat procedure was to be performed, as well the patient's overall satisfaction with the recovery process. A retrospective chart review of these patients would be done to assess for any complications in the post procedure period, such as bleeding, hematoma formation, pseudo-aneurysm, arterio-venous fistula etc. Other parameters to be measured include the time to achieve hemostasis, time to ambulate and length of hospital stay. These parameters are all recorded in the patient's clinical record as part of the standard of care.

F. Risk/benefit assessment:

Patients in this registry will not be exposed to any additional procedural risks as all treatments are in accordance with accepted clinical practice. The only potential risk would be a breach of Protected Health Information (PHI) confidentiality.
The potential benefit of participating in the study would be for the future patients undergoing catheter ablation procedures for atrial fibrillation and atrial flutter.

G. Location where study will be performed:

The morning after the procedure, patients in the cardiovascular recovery unit will be requested to fill out informed consent documents, followed by a survey (Appendix A). Each survey will be assigned a randomly generated confidential ID number and the data from the survey will be entered and analyzed into a spreadsheet that does not contain any patient identification information. A separate password protected spreadsheet will be maintained with an index of the randomly generated confidential ID numbers and the corresponding patient name and date of birth, however this will be stored separately and only the principal investigator will have access to this file.

H. Collaboration (with another institution, if applicable): N/A

I. Single IRB Review for a Multi-site study (if applicable): N/A

J. Community-Based Participatory Research (if applicable): N/A

K. Personnel who will conduct the study, including:

1. Indicate, by title, who will be present during study procedure(s): Sanjaya Gupta, MD
2. Primary responsibility for the following activities, for example:
3. Determining eligibility: Sanjaya Gupta, MD
4. Obtaining informed consent: Rakesh Ponnapureddy, MD
5. Providing on-going information to the study sponsor and the IRB: EP Research Coordinator and Regulatory Specialist
6. Maintaining participant's research records: EP Research Coordinator
7. Completing physical examination: Sanjaya Gupta, MD
8. Taking vital signs, height, weight: Rakesh Ponnapureddy, MD
9. Drawing / collecting laboratory specimens: N/A
10. Performing / conducting tests, procedures, interventions, questionnaires: Rakesh Ponnapureddy, MD
11. Completing study data forms: Rakesh Ponnapureddy, MD
12. Managing study database: Rakesh Ponnapureddy, MD

L. Assessment of Subject Safety and Development of a Data and Safety Monitoring Plan

III. Subject Participation

A. **Recruitment**: The morning after the procedure, Dr. Ponnapureddy will approach patients who underwent an ablation on the previous day and provide detailed information about the registry to the patients.

B. **Screening Procedures or Interview/questionnaire**: N/A

C. **Informed consent process and timing of obtaining of consent**

If the patient is agreeable to participate, Dr. Ponnapureddy will request they fill out informed consent documents, followed by a survey (Appendix A). Patients will not be coerced into participation and it will be emphasized to the patient that participation is voluntary. If patients are unable to provide informed consent due to cognitive or psychiatric impairment, they will not be enrolled in the registry.

D. **Alternatives to Participation**: If patients decline participation, they will continue to receive post-procedure care in the usual manner.

E. **Costs to Subjects:** There are no costs to the subject that could be incurred as part of this research study

F. **How new information will be conveyed to the study subject and how it will be documented:** If new information becomes available that may potentially impact the study subject, they will be notified by the principal investigator, Dr. Sanjaya Gupta.

G. **Payment, including a prorated plan for payment:** Patients will not receive any payment for the study.

H. **Payment for a research-related injury**: There is no possibility of injury in this study.

IV. Data Collection and Protection

A. **Data Management and Security:** The morning after the procedure, patients will be requested to fill out informed consent documents, followed by a survey (Appendix A). This survey will include parameters such as their perception of pain following the procedure, discomfort experienced, any complications that may have occurred after the procedure, their preference if a repeat procedure was to be performed, as well

the patient's overall satisfaction with the recovery process. Each survey will be assigned a randomly generated confidential ID number and the data from the survey will be entered an analyzed into a spreadsheet that does not contain any patient identification information. A separate password protected spreadsheet will be maintained with an index of the randomly generated confidential ID numbers and the corresponding patient name and date of birth, however this will be stored separately and only the principal investigator will have access to this file. Once the survey data has been entered and confirmed, the original survey will be destroyed. A retrospective chart review of these patients would also be done to assess for any complications in the post procedure period, such as bleeding, hematoma formation, pseudo-aneurysm, arterio-venous fistula etc. Other parameters to be measured include the time to achieve hemostasis, time to ambulate and length of hospital stay. These parameters are all recorded in the patient's clinical record as part of the standard of care. All documentation related to the procedure will keep in a locked, secure file cabinet at St. Luke's Hospital and/or an encrypted, protected electronic storage device that can only be accessed by participating investigators.

B. Sample / Specimen Collection: N/A

C. Tissue Banking Considerations: N/A

D. Procedures to protect subject confidentiality: All documentation related to the procedure will be kept in a locked, secure file cabinet at St. Luke's Hospital and/or encrypted, protected electronic storage device that can only be accessed by participating investigators.

E. Quality Assurance / Monitoring

1. At the time of data collection, Drs. Gupta and Ponnapureddy will review the data together to ensure that it is entered correctly from the survey into the spreadsheet. Any discrepancy will be analyzed before the original paper form is discarded.

V. Data Analysis and Reporting

A. Statistical and Data Analysis: Categorical variables will be compared with Chi-Square analysis. The patient factors that may contribute to the outcomes listed

below will be analyzed via logistic regression with subsequent multivariate logistic regression designed to compare these risk factors.

B. Outcome: The main outcomes of interest are

Perception of pain during recovery process
Overall satisfaction with recovery process
Time to achieve hemostasis
Time to ambulate following hemostasis
Bleeding and vascular complications
Need for additional manual compression following initial hemostasis
Use of protamine sulfate to reverse anticoagulation
Length of hospital stay

We expect patients who received the vascular closure device to have a reduced perception of pain, increased overall satisfaction, reduced time to achieve hemostasis, reduced time to ambulate following hemostasis, reduced bleeding and vascular complications, reduced need for additional manual compression following initial hemostasis and reduced length of hospital stay.

I. Study results to participants: If new information becomes available that may potentially impact the study subject, they will be notified by the principal investigator, Dr. Sanjaya Gupta.

J. Publication Plan: The intent is to publish this study in a peer-reviewed cardiology journal

VI. Bibliography / References / Literature Cited

1] Dauerman HL, Applegate RJ, Cohen DJ. Vascular closure devices: the second decade. *J Am Coll Cardiol*. 2007;50(17):1617-1626.
2]Koreny M, Riedmuller E, Nikfardjam M, Siostrzonek P, Mullner M. Arterial puncture closing devices compared with standard manual compression after cardiac catheterization: systematic review and meta analysis. *JAMA*. 2004. 291930:350-357.

3] Biancari F, D'Andrea V, Di Marco C, Savino G, Tiozzo V, Catania A. Meta-analysis of randomized trials on the efficacy of vascular closure dvices after diagnostic angiography and angioplasty . *Am Heart J*. 2010;159(4):518-531.
4]Nikolsky E, Mehran R, Halkin A, et al. Vascular Complications Associated With Arteriotomy Closure Devices in Patients Undergoing Percutaneous Coronatry Procedures. A meta analysis. J Am Coll Cardiol 2004;44:1200.
5] Stefanie Schulz-Schüpke, MD[1,2]; Sandra Helde, cand med[1]; Senta Gewalt, cand med[1]; et al. Comparison of Vascular Closure Devices vs Manual Compression After Femoral Artery Puncture. The ISAR-CLOSURE Randomised Clinical Trial. *JAMA*. 2014;312(19):1981-1987. doi:10.1001/jama.2014.15305
6] Vaitkus PT. A meta analysis of percutaneous vascular closure devices after diagnostic catheterization and percutaneous coronary intervention. J Invasive Cardiol 2004;16:243-246.
7] Maraj I, Budzikowski AAS, Ali W, Mitre CA, Kassotis J. Use of vascular closure device is safe and effective in electrophysiological procedures. J Interv Card Electrophysiol. 2015. Aug;43(2):193-5. doi: 10.1007/s 10840-015-0005-5. Epub 2015 Apr 29.
8]Abo-Salem E, Miller B, Wexler L, Attari M. Vascular Closure Devices for venous accesses in anticoagulated patients after catheter ablation for Atrial Fibrillation. JACC March 17,2015. Volume 65, Issue 10S.
9] Martin J, Pratsos A, Magargee E, Mayhew K, Pensyl C, Nunn M, Day F, Shapiro T. A Randomised Trial Comparing Compression, Perclose Proglide and Angio- Seal VIP for Arterial Closure Following Percutaneou Coronary Intervention: The CAP trial. Catheterisation and Cardiovascular Interventions 71:1-5 (2008)
doi 10.1002/ccd.21333
10] Noguchi T, Miyazaki S, Yasuda S, Baba T, Sumida H, Morii I, Daikoku S, Goto Y, Nonogi H. A randomized Controlled Trial of Prostar Plus for Haemostasis in Patients After Coronary Angioplasty. Eur J Vasc Endovasc Surg 19,451-455(2000)
doi:10.1053/ejvs.1999.1071.
11] Duffin DC, Muhlestein JB, Allisson SB, et al. Femoral arterial puncture management after percutaneous coronary procedures: a comparison of clinical outcomes and patient satisfaction between manual compression and two different vascular closure devices. *J Invasive Cardiol* 2001;13:354-62.
12] Aytemir K, Canpolat U, Yorgun H, Evranos B, Kaya EB, Sahinger ML, Ozer N. Usefulness of 'figure-of-eight' suture to achieve haemostasis after removal of a 15-French calibre femoral venous sheath in patients undergoing cryoablation. Europace 18(10), 1545-1550 (2016)

Post Ablation Procedure Patient Survey

(please circle one answer per question)

Confidential ID: _____

1. **Please rate your pain during post-procedure recovery period, was your pain:**

Much worse than anticipated	Worse than anticipated	About what you anticipated	Better than anticipated	Much better than anticipated

2. **Please rate your discomfort experienced while walking after your procedure. Was it:**

Much worse than anticipated	Worse than anticipated	About what you anticipated	Better than anticipated	Much better than anticipated

3. **Please rate your overall satisfaction with your post-procedure recovery. Are you:**

Extremely dissatisfied	Dissatisfied	Neither satisfied or dissatisfied	Satisfied	Extremely satisfied

4. **Have you had an ablation procedure in the past, which was followed by manual compression at the groin site?**

Yes	No

A. If you answerd yes, and if you had a closure device used for this procedure, would you prefer this method over manual compression:

Yes	No

5. **Please rate your level of concern for having a bleeding event after the procedure, are you:**

Extremely concerned	Very concerned	Concerned	Slightly concerned	Not concerned

6. **Would you have been comfortable being discharged home, about 4 hours after you were allowed to sit up, on the same day as your ablation?**

Yes	No

7. **Please write any additional comments regarding your post-procedure recovery below:**

_____

_____

_____

_____

Thank you for your participation in this survey.