COVER PAGE

STUDY TITLE: Suture closure AFtEr VEIN access for cardiac procedures (SAFE-VEIN) Trial: A randomized, prospective study of the safety and efficacy of venous closure device compared to conventional closure strategies in post venous access procedures

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PROTOCOL TITLE:

Suture closure AFtEr VEIN access for cardiac procedures (SAFE-VEIN) Trial: A randomized, prospective study of the safety and efficacy of venous closure device compared to conventional closure strategies in post venous access procedures.

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I. Background and Rationale

Venous access is commonly used in interventional catheter procedures such as atrial fibrillation (AF) ablation, WATCHMAN™ device placement, and Patent Foramen Ovale (PFO) closure. Access site bleeding and hematoma are anticipated vascular complications post procedure, and risk of complications may rise with a longer time to hemostasis (TTH). Two conventional method closure strategies (1) that are usually used for hemostasis in these procedures are:

1. figure 8 suture and
2. manual compression.

Using a vascular closure device to achieve hemostasis has been shown to shorten time to both hemostasis and ambulation as well as improve patient comfort and satisfaction (2). Perclose ProGlide Suture-Mediated Closure System (SMC) is a commonly used vascular closure device for arterial closure and is approved by FDA for percutaneous closure of femoral artery and vein access sites (3). Perclose ProGlide SMC has been shown to be safe with low incidence of vascular complication (3,4) and reduce the time to hemostasis (3). The device has been shown in a small study to lower the time to ambulation and shorten the length of stay compared to manual compression (5). To our knowledge, there have been no studies published that compare efficacy and safety of Perclose ProGlide SMC vs. figure 8 suture method.

II. Objectives and Specific Aim

Primary objective: To compare the safety and efficacy of closure strategies post venous access procedures in large-bore venous access procedures.

Hypothesis: We anticipate that the use of a venous closure device will decrease the time to hemostasis (TTH), time to ambulation (TTA) and time to discharge (TTD) compared to conventional methods of closure following venous access procedure.

III. Study Design & Methodology

This study will be a prospective, randomized study of patients who are undergoing one or more of the following procedures at ASLMC:

Large-Bore Procedures >13 F

1. WATCHMAN® device placement
2. Atrial fibrillation/flutter/SVT ablation using cryoballoon or laser balloon
3. Leadless pacemaker
4. Pulmonary embolism thrombectomy (Inari FlowTriever system)
5. MitraClip transcatheter mitral valve repair

RANDOMIZATION:

Patients will be randomized into one of two venous closure groups after a clean stick has been achieved with no complications:

Large-bore (14F-25F) venous access group (1:1)
Perclose proglide smc
Figure 8 suture

Prior to enrollment a series of 110 randomization envelopes will be put together in a 1:1 to determine the closure strategy – Figure 8 suture or Perclose ProGlide SMC closure device for the large-bore procedures. Study investigators will draw an envelope to determine what group the subject will be randomized to only after sheath access has been achieved with no complications. Access should be ultrasound guided to guarantee a clean stick.

If randomization does not occur or if a complication not related to the Perclose ProGlide SMC closure device happens during the procedure the subject will be withdrawn from the study and considered a screen failure.

For both Perclose ProGlide SMC and figure 8 suture, supplemental manual compression may be used following device/suture placement if needed. If at any time the physician decides to use an alternate standard of care method as the primary method to achieve hemostasis other than that which the patient was randomized to, they may do so, and the patient will be considered a screen failure.

We will collect demographic data, past medical history, medication at the time of procedure, lab values at the time of procedure and post procedure, the need for blood transfusion, procedure details, and outcomes post procedure. *Study variables are listed in detail in the attached Excel file.*

Table 1: Schedule of Study Events:

Study Procedure	Screening	Day of Procedure	Follow-up (30 days post procedure)
Inclusion/exclusion	X		
Informed Consent		X	
Randomization to determine closure strategy		X	
Data collection (medical history/baseline demographics, medications, lab values, procedure details, and outcomes post procedure)		X	X

IV. **Eligibility**

Inclusion criteria:

Large-bore (>13F) Venous Access Procedures Inclusion Criteria:

All patients 18 years and older who are undergoing any of the following: WATCHMAN® device placement, atrial fibrillation ablation using cryoballoon or laser balloon, leadless pacemaker, Pulmonary embolism thrombectomy (Inari FlowTriever system), MitraClip transcatheter mitral valve repair at Aurora St. Luke's Medical Center from date of IRB approval through December 2022. All arterial line access should be radial.

Exclusion criteria:

Large-bore (>13F) Venous Access Procedures Exclusion Criteria:

- **Patients in whom introducer sheaths >25F were used in the vein during the catheterization procedure.**
- Patients with small femoral arteries or veins (< 5 mm in diameter).
- Patients with access sites in vascular grafts.
- Patients with intra-procedural bleeding around access site. Patients who cannot receive radial arterial line access.
- Patients who have complications during the procedure not related to the Perclose ProGlide SMC closure device
- The physician determines that they must use an alternate method as the primary venous closure method other than that which the patient was randomized to
- Active systemic or cutaneous infection, or inflammation in vicinity of the groin
- Pre-existing immunodeficiency disorder or chronic use of high dose systemic steroids
- Known history of bleeding diathesis, coagulopathy, hypercoagulability or platelet count < 100,000 cells/mm3
- Severe co-existing morbidities with life expectancy less than 12 months

- Femoral arteriotomy or femoral venotomy in < 10 days, or with any known vascular complications or residual hematoma, or with use of an intravascular closure device w/in previous 30 days
- Planned femoral venous or arterial access within next 30 days
- Unable to routinely walk at least 20 ft. without assistance
- LMWH within 8 hours before or after procedure
- Pregnant and/or lactating women
- Extreme morbid obesity (BMI > 40 kg/m2) or underweight (BMI < 20 kg/m2)

V. Subject Enrollment

Recruitment and consent are required since it is a prospective study. Patients will be identified for potential enrollment in this study from the lab schedules at Aurora St. Luke's Medical Center. The potential subjects medical record will be screened to determine eligibility. Patients found to be eligible will be considered for enrollment and may be contacted prior to the procedure to assess interest in participation.

VI. Specimen/Data Collection and Procedures

The source of data for this study will be the electronic medical record (Epic, Madison, WI). Only people included in this IRB will access the compiled data. Medical record information generated after the approval of this IRB will be collected up until the conclusion of the study.

VII. Risks, Protection & Benefits

Risks/adverse events as reported in the IFU – these complications may occur and/or be related to the procedure or the vascular closure:

- Allergic response
- Anemia
- Arterial stenosis/occlusion
- Arterio-venous fistula
- Bleeding from the puncture site
- Bruising/hematoma
- Death
- Device failure/malfunction/misplacement
- Device Entrapment
- Diminished pulses distal to closure site
- Hypotension/hypertension
- Edema
- Embolism
- Pulmonary Embolism
- Numbness
- Infection/sepsis
- Inflammatory response
- Intimal tear/dissection
- Ischemia distal to closure site
- Perforation of the vessel wall
- Nerve injury
- Pseudoaneurysm
- Retroperitoneal hematoma/bleeding
- Deep vein thrombosis
- Vascular injury
- Vasovagal episode
- Vasoconstriction/vasospasm
- Wound dehiscence
- Pain

- Thrombus formation

Risks of figure 8 suture method:

- Pain
- Pressure
- Hematoma
- Bleeding
- Vessel rupture
- Surgery

Benefits:

Depending on the closure strategy subjects may experience a decrease in bedrest time post procedure with potentially less complications.

Results of this study may also be generalizable to the larger healthcare community by informing standard of care guidelines for obtaining hemostasis and post procedure outcomes following the procedures studied in this protocol.

VIII. Adverse Event Reporting

a. Definitions

Adverse event: Any untoward medical occurrence, unintended disease or injury or untoward clinical signs in subjects, users, or other persons, whether or not related to the medical device.

Serious adverse event: Any adverse event that led to

- Death
- Life-threatening illness or injury
- Permanent impairment
- Prolonged hospitalization or change to inpatient status
- Requires medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment
- Fetal distress, fetal death, or congenital abnormality or birth defect

b. Reporting Requirements

All observed or volunteered adverse events occurring from the time of randomization to 30-days post randomization will be recorded in the subjects' case histories, regardless of the study group or suspected causal relationship. For all adverse events, sufficient information will be obtained in order to permit: 1) adequate determination of the seriousness, and 2) causal relationship of the adverse event. Adverse events or serious adverse events found to be a result of the treatment regimen will be followed until resolution of the adverse event.

Reportable adverse events include:

- Excessive Bleeding
- Hematoma
- Ischemia
- Infection
- Rash at access site

All adverse events and serious adverse events are to be reported to the Aurora Health Care Internal Review Board as outlined in the applicable policies.

c. Assessment of Relationship

The Principal Investigator is responsible for assessing the relationship of the adverse event or serious adverse event to the treatment.

IX. Data Analysis and Review

Continuous variables will be presented as means and standard deviation or median and interquartile ranges if normality is not assumed. Baseline demographic and medical data will be summarized and compared by standard descriptive statistical methods (ANOVA for continuous variables and Chi squared test for categorical variables or their non parametric equivalents). Comparisons will be made among groups based upon clinical factors using univariate regression to select potential independent predictors of outcomes (as defined in section III of the current document). Relevant potential independent predictors as determined by univariate analyses and expert clinical knowledge will then be included in multivariate regression models. Assumptions and goodness of fit will be assessed for each model. Statistical significance will be defined as a two tailed p value < 0.048 at final analysis. Further data analysis will be performed by clinical statistician (TBD).

A stratified analysis by French size or procedure type will be considered if there is evidence to suggest one is needed.

An interim monitoring plan to perform periodic checks of the data after the first 25 subjects are enrolled and then again after 75 subjects are enrolled will be reviewed by the Biostatistician or study team to determine data integrity, accuracy, and consistency with the study objectives/hypotheses as well as preliminary analysis.

X. Statistical Considerations

A convenient sample size of approximately 55 subjects in each of the two randomized groups (Perclose ProGlide SMC and figure 8 suture) was determined to allow for parametric statistical methods. Following interim analysis: O'Brien-Fleming method was selected to adjust the p-value for interim analysis and final analysis. It was also used to calculate the required sample size at each stage of analysis in order to achieve 80% power in the outcome. Final sample size required was determined at 101 subjects. A 10% +/- should be added, to bring the total enrollment to 110 subjects.

XI. Outcomes

Primary outcomes: time to achieve hemostasis (TTH) and time to ambulate (TTA)
Secondary outcomes: time to discharge (TTD)/length of stay, post procedure major bleeding, mortality due to vascular complications, minor bleeding, access site hematoma, vascular thrombosis, vascular dissection, pseudoaneurysm, or AV fistula.

TTH: The elapsed time between "device" removal and first observed and confirmed venous hemostasis.

TTA: The elapsed time between removal of the final Perclose ProGlide SMC device (treatment arm) or removal of the final sheath (control arm), and the ability of subjects to stand and ambulate 20 feet without evidence of venous re-bleeding from the femoral access sites.

TTD/LOS: The elapsed time between removal of the final sheath, and the ability of subjects to be discharged. Length of hospital stay.

Major bleeding: Bleeding associated with ≥2 g/dl drop in hemoglobin level requiring transfusion, bleeding that occurs at a critical site, or bleeding contributing to death.

Minor Bleeding: Any bleeding that does not meet the criteria for major bleeding.

XII. Regulatory Requirements

Approval from the Aurora Health Care IRB will be obtained to perform this study, which includes approval of all associated informed consent forms. All protocol modifications and corresponding informed consent forms will be submitted for review and approval prior to implementing.

The Principal Investigator is responsible for ensuring that all study personnel have appropriate training and experience to perform the assigned duties.

The Principal Investigator will ensure that the study is performed in accordance with the approved protocol, and will document and report protocol deviations as required by the Aurora Health Care IRB policies.

XIII. Monitoring Plan

The goal of monitoring in this study is primarily to make sure that the primary data are collected and recorded properly, and consenting process was done.

The Principal Investigator will be responsible for monitoring the safety environment of the participants, and will ensure that

a) Only subjects who meet the study eligibility criteria will be enrolled. All subject inclusion/exclusion criteria were reviewed and verified with source documents, when applicable.

b) The informed consent process will be obtained prior to proceeding with any study procedures. Any problems with informed consent will also be documented, and reported to the IRB, if required.

c) Data is collected and analyzed as specified in the protocol.

d) Adverse events are reviewed promptly and reported as required.

e) Privacy and confidentiality of subjects is maintained. Consent forms will be stored in a room accessible only to research personnel.

f) Subject withdrawals will be documented for the reason of withdrawal.

g) Subjects will be informed during the informed consent process that study results may be disseminated in the form of presentations at conferences and publications in journals. The data/results that will be presented will only include anonymous/aggregate data, nothing that will identify subjects.

h) A regulatory binder will be kept to document: IRB approvals, protocol versions, informed consents (all versions), all formal communications with the IRB (approval letters, acknowledgements), Delegation of Authority Log.

XIV. References

1. U. Lakshmanadoss et al. Figure-of-eight suture for venous hemostasis in fully anticoagulated patients after atrial fibrillation catheter ablation. Indian Pacing and Electrophysiology Journal 17 (2017) 134e139
2. PMA P960043/S097: FDA Summary of Safety and Effectiveness Data
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4. Vinayakumar D, Kayakkal S, Rajasekharan S, Thottian JJ, Sankaran P, Bastian C. 24h and 30 day outcome of Perclose Proglide suture mediated vascular closure device: An Indian experience. *Indian Heart J*. 2017;69(1):37-42. doi:10.1016/j.ihj.2016.06.008
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