A RANDOMIZED COMPARISON OF PERCUTANEOUS CLOSURE TO MANUAL COMPRESSION FOR HEMOSTASIS OF MULTIPLE VENOUS ACCESS SITES AMONG PATIENTS UNDERGOING CATHETER ABLATION FOR ATRIAL FIBRILLATION

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Full Study Title: A randomized comparison of percutaneous closure to manual compression for hemostasis of multiple venous access sites among patients undergoing catheter ablation for atrial fibrillation.

Short Study Title: PerClose Proglide

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Introduction/Backround:
Radiofrequency ablation for treatment of atrial fibrillation (AF) using percutaneous venous access at the groin is one of the most common procedures performed by cardiac electrophysiologists[1]. However, compared to other catheter-based interventions, patients undergoing AF ablation pose a unique set of challenges. First, AF ablation requires multiple points of transfemoral venous access with large diameter sheaths, ranging in size from 8F to 14F for cryoablation procedures. Second, operators are forced to balance the competing risk of thrombosis and bleeding in these patients. In order to minimize the risk of intraprocedural thrombosis, anticoagulation with heparin with a goal anticoagulation time (ACT) >300-350 seconds is necessary[2]. However, operators typically require ACTs to normalize prior to removal of sheaths and manual compression, which significantly delays hemostasis and ambulation. While reversal agents are an option, there is currently clinical equipoise on their role and safety in this setting[3] and they require additional time to exert their full effect. Lastly, patients require at least 1-2 months of therapeutic oral anticoagulation after the procedure to mitigate ongoing stroke risk[1]. These factors culminate in longer times to hemostasis and ambulation and raise concerns for post-procedure access related complications for patients undergoing AF ablation. PerClose Proglide™ has recently gained FDA approval for closure of percutaneous venous access sites for catheter-based interventions and remains the only commercially available solution for access sites >14F inner diameter. Percutaneous closure of venotomy sites may facilitate rapid hemostasis without the need for reversal of anticoagulation, potentially attenuating bleeding risk. Additionally, typical bedrest times after percutaneous closure are based on data derived from arterial closure. Prior limited data[4], as well as frequent anectodical reports, have suggested that earlier ambulation may be feasible. Because the venous circulation is a lower pressure system, it is possible that earlier than standard ambulation times after PerClose is both safe and feasible. However, a rigorous prospective investigation of the PerClose Proglide™ device in the context of AF ablation has not been performed.

Objectives/Hypotheses:
We hypothesize that, among patients undergoing ablation for AF, percutaneous closure of access sites with PerClose Proglide™ will lead to shorter times to hemostasis as compared to manual compression. Our secondary hypothesis is that patients undergoing PerClose after AF ablation, will be able to safely ambulate at one hour, as opposed to two hours, after hemostasis. We will also evaluate several other secondary endpoints comparing those undergoing PerClose to those undergoing manual hemostasis including: frequency of access site related complications, pain and need for post-procedure narcotics, patient satisfaction, as well as cost and overall resource utilization.

Research Design:
The study will occur in patients undergoing routine ablation for atrial fibrillation as standard of care. This is a prospective randomized trial. Patients will be randomized (see Randomization) in a 1:1 ratio to either manual compression or use of the PerClose for hemostasis at the end of the ablation procedure. Based on our clinical experience, we estimate the PerClose procedure for 3 access sites will require ~3 minutes of additional procedure time. In our experience, hemostasis is typically immediate (<1 minute to lock all three sutures) and this corroborated in the available literature[5]. Prior published data for manual compression with figure-of-eight sutures are reported as 7.9 minutes[6]. We also intend to have a secondary treatment arm in which post-hemostasis

ambulation time will be one hour (currently, the standard is two hours after vascular closure). The length of follow-up will be up to 30 days at routine clinical follow-up after the procedure.

Patient Selection:
Study patients will be recruited among all patients older than 18 years old undergoing elective atrial fibrillation ablation at Emory University Hospital, Emory University Hospital Midtown, or Emory St. Joseph's Hospital. Exclusion criteria are: 1) women who are pregnant (based on standard pre-procedure pregnancy test); 2) patients who are not able to ambulate pre-procedure; or 3) patients who are unable to provide informed consent.

Pilot Cohort:
In order to demonstrate feasibility, we propose an initial pilot cohort of 50 patients (25 patients in each group). The purpose of this cohort is to demonstrate feasibility of patient enrollment, data collection, and produce initial pilot data. This cohort is not anticipated to be sufficiently powered to evaluate the primary endpoint definitively. However, it is likely than any trends in data would become apparent with a cohort of this size.

Full Study Cohort:
Based on these estimates, we preliminarily calculated a sample size of 100 patients (50 in each arm, including the pilot cohort) to achieve an alpha-level of 0.05 with a beta-level of 0.2 (power of 80%). We would argue for a goal of approximately 65 patients in each arm to account for loss to follow up at the 30-day period, for a goal total of 130 patients enrolled.

Data to be collected:
Baseline Clinical Information:
Routine baseline clinical characteristics including preprocedural oral anticoagulation regimen, antiplatelet regimen, and INR for those on warfarin therapy as are routinely collected as part of standard care.

Procedural data will include*:*
- Time to hemostasis
- Case length (routinely collected)
- Anticoagulation time (ACT) at the completion of the case prior to sheath pull (routinely collected)
- Success rate of PerClose™ deployment and number of PerClose™ devices used.
- Success rate of hemostasis with manual compression or "figure-of-eight" suture.

Post procedural data collected will include:
- Time to ambulation after ablation
- Major and minor* access related complications prior to discharge, at 48 hours, and at 30 day follow up appointment:
    - Superficial bruising
    - Hematoma
    - Retroperitoneal bleeding
    - Hemorrhage of any kind
    - Need for transfusion of blood products

    - Pain (see below).
    - Presence of post-procedure venous thromboembolism

  *A major complication would be defined as the following: management, at the discretion of the treating physician, requiring direct procedural or medical intervention (other than observation) for any complication noted above.
- Groin access site pain as measured by:
    - A 10-point visual analog scale (0 = none; 10 = worst imaginable) on discharge, as validated in the PEVAR trial[7], and is already routinely used at our institution.
    - By short form inguinal pain questionnaire on 30-day follow up[8].
    - Opiate medication requirement prior to discharge (total dosage to be standardized to milligrams of morphine).
    - Opiate medication prescription on discharge (binary).
- Economic and cost data related to:
    - The cost of the PerClose devices used.
    - Ancillary resource utilization (i.e. devices used for hemostasis, sutures for "figure of eight", cost of protamine for heparin reversal if used)
    - Length of stay
    - Post-procedure area time
    - Access site complication related cost including imaging required for workup and any interventions for management including medications administered or procedure charges.
- Nursing utilization (number of nursing encounters while in the post procedure area [routinely collected]).

Randomization:
Patients will be randomized in two one of two groups: those undergoing percutaneous closure with PerClose™ and those with manual compression (manual hemostasis with, or without "figure of eight" suture[6] for hemostasis at the discretion of the treating physician). Patients will be randomized in a 1:1 ratio to groups and stratified on sex to ensure equal proportions of males and females in both groups. Block randomization with block sizes of 6 will be used. Blocks will be generated as needed using a computer model. In the PerClose arm, patients will be randomized secondarily in 1:1 fashion as either standard ambulation (2 hours bed rest) or early ambulation (1-hour bedrest) after hemostasis.

Informed Consent:
Following education on the study protocol, patients will be offered the option to enroll. Informed consent will be obtained by approved research personnel in a private area. If the patient agrees to participate, consent will be documented. Consent will occur the day of the scheduled ablation procedure.

Compensation for time and effort:
There is no compensation for participation in this study as there are no additional expenses and time requirement beyond standard of care.

Risks/Benefits:

The most common risks and discomforts expected in this study are rare but possible: development of a blood clot in the leg (less than 1%), bleeding (less than 1%) or a large bruise called a hematoma at the IV site (less than 1%).

Possible benefits, although unproven, may include less time in the post-procedure area and the ability to walk sooner after the ablation procedure. This study is designed to learn more about the use of percutaneous closure with the PerClose Proglide™ after atrial fibrillation ablation. The study results may be used to help others in the future.

Data Analysis:
The primary endpoint of the study will be time to hemostasis (starting from sheath pull) in minutes for the PC and MC groups. The secondary endpoints will include: 1) time to ambulation in minutes, 2) a composite of all major access site complications and venous thromboembolism, 3) each individual outcome comprising the composite outcome, 4) minor complications, 5) quality of life metrics (as measured by the inguinal pain questionnaire), 6) procedure length in minutes, 7) patient satisfaction , 8) pain medication requirement after hemostasis until discharge from the post-procedure area, 9) overall cost comparison related to hemostasis and complications over 30 days, 10) number of nursing encounters while in the post-procedure area. We will also compare all secondary endpoints between the primary and secondary treatment arms. Access related complications include: hematoma, hemorrhage, retroperitoneal bleeding, pseudoaneurysm, arteriovenous fistula, or access site infection. Thromboembolism will include any arterial or venous thromboembolism that are clinically overt. Major complications will be defined as any of the above pre-specified complications that require direct procedural intervention (surgical or percutaneous repair), placement of an external compression hemostatic device (i.e. pneumatic compression dressing or femoral compression device), or medical therapy (including, but not limited to transfusion, reversal of anticoagulation, or initiation of other new medical therapy). Minor complications will include any complication that does not require any intervention beyond observation.

Normality of distribution of continuous variables will be tested using the Shapiro-Wilk test. Comparisons of continuous baseline variables across groups will be performed using Student's t and Mann-Whitney U tests for normally and non-normally distributed data, respectively. Comparison of categorical variables will be performed using Chi-squared and Fisher's Exact tests for binary categorical variables where appropriate, and Mann-Whitney U test for ranked ordinal level variables. Complication-free survival will be evaluated using Kaplan-Meier analysis, with separate strata for patients in each group. Patients will be censored at the time of their last confirmed encounter or at the completion of the follow up time of the study. All analyses will be performed using IBM SPSS ver. 25 (2017; IBM SPSS Statistics for Macintosh, Version 25.0. Armonk, NY: IBM Corp).

Safety analysis:
Safety assessments will consist of monitoring and recording all adverse events and serious adverse events. While they are not anticipated, adverse events will be summarized using the frequency of subjects for each level.

Data and Safety Monitoring and Reporting:

Oversight of the progress and safety of the trial will be provided by the PI. Adverse events are not anticipated, but any occurring will be reported to Emory IRB policies and procedures.

Confidentiality:
Patients will be assigned an identifier number. Data will be stored on a secure drive supported by Emory healthcare. Only pertinent members of Emory Healthcare/ SOM who have undergone HIPAA training will have access to the spreadsheet. PHI information including the informed consent forms will be stored in a locked space in the PI's office.

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