Protocol:

Left Atrial Posterior Wall Isolation in Conjunction with Pulmonary Vein Isolation for Treatment of Persistent Atrial FibrilLation (PIVoTAL) Trial

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2 STUDY ENDPOINTS

2.1 PRIMARY EFFICACY ENDPOINT

(i) To determine whether posterior left atrial wall (PLAW) isolation in conjunction with pulmonary vein isolation (PVI), as compared to PVI alone, can yield a reduction in atrial arrhythmia recurrence at 1 year in patients with persistent/long-standing persistent atrial fibrillation (AFp) undergoing catheter ablation therapy

2.2 PRIMARY SAFETY ENDPOINT

(i) To evaluate the overall complication rate associated with PLAW isolation in conjunction with PVI as compared to PVI alone, in patients with AFp undergoing catheter ablation therapy

3 INTRODUCTION, RATIONALE AND OBJECTIVE

Catheter ablation has emerged as a safe, practical and effective strategy for treatment of atrial fibrillation (AF), with pulmonary vein isolation (PVI) as the primary cornerstone of this strategy. On the other hand, the success rate associated with catheter ablation of persistent/long-standing persistent AF (AFp) remains significantly lower than that of paroxysmal AF, with wide variations in the ablation technique among different operators[1]. To date, several studies have prospectively examined the impact of substrate (complex fractionated electrogram) and linear ablation[2,3,4]. Yet, none of these studies have found a clear benefit associated with either approach over PVI, alone. Meanwhile, some investigators contend that the mechanism for maintenance of AFp may be inherently different from that of paroxysmal AF, implicating the posterior left atrial wall (PLAW) as a potential culprit[5]. Along these lines, Corradi et al.[6] discovered an increased incidence of PLAW structural remodeling using light microscopy in patients with as opposed to those without AFp. Similarly, Cutler et al.[5] found that the presence of PLAW scar served as an important ablation target in patients with AFp.

The PLAW implication in patients with AFp is in fact plausible, as this structure shares its embryological origins with the primordial pulmonary veins[7]. As such, a number of studies and published reports have previously described the presence of rotors and spontaneous triggers within the PLAW[8,9,10]. Moreover, several small-sized and/or single-center studies have illustrated the feasibility[11,12,13] and even the potential benefit[14,15,16,17] associated with electrical isolation of the PLAW in conjunction to PVI in AFp patients undergoing catheter ablation therapy. However, presently there is a paucity of randomized-controlled data to address the role for such an approach. Thus, the aim of this multicenter, randomized-controlled trial is to prospectively compare and analyze the approach of PVI with or without PLAW isolation in a large cohort of patients with symptomatic AFp.

4 STUDY DESIGN

Patients with symptomatic AFp undergoing catheter ablation of AF will be randomized to either PVI alone (Group 1) or PVI + PLAW isolation (Group 2).

5 STUDY SUBJECTS

5.1 INCLUSION CRITERIA

In total, 200 patients with symptomatic AFp will be enrolled in this multicenter, randomized, prospective, single-blinded study. Consistent with the current definitions[18], all patients with persistent AF must have ≥1 documented episode of AF lasting >1 week in duration or lasting <7 days but requiring electrical/pharmacological cardioversion to sinus rhythm. Patients with long-lasting persistent AF will be defined as those with continuous AF of >1 year duration.

- Males and females with an age >18 years undergoing a first-time catheter ablation of AF; prior ablation of a right atrial cardiac arrhythmia (i.e., typical right atrial flutter) is permitted
- All patients must understand the requirements of the study and be willing to comply with the post-study follow-up requirements
- Patients must be in AF on the day of the procedure

5.2 EXCLUSION CRITERIA

- Any reversible cause of AF (post-operative, thyroid disorder, etc)
- Patients with cerebral ischemic events (stroke or transient ischemic attack), myocardial infarction or unstable angina in the previous 2 months
- Patients with complex congenital heart disease
- Patients with a history of hypertrophic cardiomyopathy
- Patients with cardiomyopathy and a left ventricular ejection fraction <35%
- Congestive heart failure, class IV
- Women who are known to be pregnant or have had a positive β-HCG test 7 days prior to procedure

- Patients whose life expectancy is <1 year
- History of left-sided left atrial ablation (catheter or surgically-based)
- Mental impairment precluding the patient from providing informed consent or completing appropriate follow-up

6 SAMPLE SIZE

We plan to enroll 200 patients in this multicenter, prospective, randomized single-blinded trial. Of these, 100 patients will be assigned the arm receiving PVI (Group 1) and 100 patients to the arm receiving PVI + PLAW isolation (Group 2). However, an interim analysis will be performed after enrolling the first 100 patients (50 patients in each arm) to assess for the primary efficacy and safety endpoints. Decisions regarding further enrollment will be made accordingly based on this interim analysis.

7 PATIENT ENROLLMENT AND WITHDRAWAL

Patients meeting the study inclusion criteria will be identified in the outpatient setting by one of the study sites primary or co-investigators. The study will be thoroughly described during the initial clinic visit including the potential risks and benefits. Consent will typically be obtained at the time of the initial assessment if it is clear that the patient understands the nature of the study. Alternatively, the patient will be allowed to take a copy of the consent form home to contemplate whether they would like to be enrolled in the study. A sample consent form can be found in Appendix 1. Only patients who voluntarily provide consent will be included in this study.

Of note, randomization is performed prior to the ablation procedure. Consent will be obtained prior to undergoing the ablation. Patients will be able to withdraw from the study at any point without compromising their medical care. We expect to achieve ≥90% rate of follow-up.

8 STUDY PROCEDURE

This study will evaluate a standardized approach of PVI to PVI + PLAW isolation.

8.1 PRE-PROCEDURAL EVALUATION

The following tests and procedures will occur before the ablation:

- Recording of patient medical history (including CHA2DS2-VASc score, duration of AF, number of cardioversions)
- Recording medication history (history of antiarrhythmic drugs [AADs], duration of AAD use)
- Symptom assessment using the CCS-SAF score (19) (Appendix 2).
- CT or MRI scan within six (6) months of the procedure is recommended
- Echocardiogram (preferably a transthoracic study with complete measurement of cardiac dimensions and left atrial assessment) within 1 year of the procedure
- β-HCG in women of child bearing age on the morning of the procedure

8.2 PRE-PROCEDURAL MEDICATION MANAGEMENT

- Therapeutic anticoagulation is recommended for 3 weeks prior to the procedure (if not possible, intra-procedure transesophageal or intracardiac echocardiography is recommended to exclude a left atrial thrombus)
- All AADs except amiodarone will be discontinued at least 5 half-lives prior to the procedure; amiodarone may be continued throughout the peri-procedural period

9 ABLATION DETAILS

- Patients will be taken to the electrophysiology laboratory in a fasting state
- All patients must be in AF at the start of the procedure
- General anesthesia or conscious sedation will be used at the discretion of the primary electrophysiologist
- Esophageal temperature monitoring is highly recommended

- Vascular access, number of transseptal punctures and catheter selection will be left to the discretion of the operator
- All cases will be performed utilizing 3-dimensional electro-anatomical mapping with St. Jude NavX (St. Jude Medical, Inc, St. Paul, MN)
- A post-ablation voltage map is recommended
- Circumferential PVI must be performed first
- Bi-directional block must be demonstrated following PVI before and after a drug challenge (isoproterenol or adenosine)
- Radiofrequency ablation must be performed using an irrigated-tip ablation (TactiCath or FlexAbility ablation catheters, St. Jude Medical, Inc)
- Cardioversion to ensure PVI is permitted
- Ablation of other arrhythmias inducible at the time of ablation (i.e., right- or left-sided atrial flutters) is permitted

10 RANDOMIZATION AND STUDY SITES

- Patients will be randomized prior to the procedure to either PVI (Group 1) or PVI + PLAW isolation (Group 2)
- However, the operator will be blinded to this until the completion of PVI
- Once bilateral PVI has been completed, the operator will be notified by his/her research coordinator as to whether the patient will undergo PLAW isolation
- Numbering of the subjects when completing all case report forms (CRFs):

  _1_-_2_ _3_ _4_

  1: Site number (each site will be assigned a unique number)

  2/3/4: Overall patient number (001 – 200)
- Site participating in this clinical trial include:
  1) Mercy General Hospital and Dignity Health Heart & Vascular Institute, Sacramento, CA, USA
  2) Instituto de Pesquisa em Arritmia Cardiaca, Hospital Cardiologico, Florianopolis SC, Brazil
  3) Center for Atrial Fibrillation, Hospital Pró-Cardíaco, Rio de Janeiro, Brazil

4) Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada

11 POST-PROCEDURAL MANAGEMENT

11.1 POST-PROCEDURAL FOLLOW-UP

- All patients will be monitored for a minimum of 6 hours and will typically be discharged either on the day of the procedure or the following day
- Complications (i.e., vascular, bleeding, stroke, etc) will be documented
- Patients will be instructed to call the local study coordinator or his/her cardiac electrophysiologist with any questions or concerns during the follow-up period

11.2 POST-PROCEDURAL TESTING

- Patients will receive 7–14 day ambulatory ECG monitoring at 3 months, 6 months and 13 months post-ablation, unless the patient has an existing cardiac implantable electronic device (CIED)
- Repeat echocardiographic examination to re-assess left atrial size/remodeling at 4–6 months is recommended

11.3 POST-PROCEDURAL MEDICATION MANAGEMENT

- AAD therapy should be discontinued within 3 months of the procedure, however deviation to this recommendation is permitted at the discretion of the patient's cardiologist/cardiac electrophysiologist

11.4 MANAGEMENT OF RECURRENT ATRIAL ARRHYTHMIA(S)

- A 3-month blanking period will be used when assessing the primary efficacy endpoint
- The date of documented first recurrence of atrial arrhythmia (i.e. AF, atrial flutter, etc) will be documented even if this were to occur prior to 3 months
- The date of first arrhythmia recurrence (i.e. AF, atrial flutter, etc) after the 3-month blanking period will also be documented
- Rhythm status at the end of the study period will be documented

- Management of recurrent arrhythmia will be left to the discretion of the patient's cardiologist/cardiac electrophysiologist; management options may include: changing or resumption of AAD, cardioversion, repeat ablation, etc
- Repeat ablation procedures are permitted during the blanking period
- The ablation strategy for a repeat procedure will be left to the discretion of the primary cardiac electrophysiologist
- All findings (including the presence of PVI durability and PLAW isolation if applicable) and details of the repeat ablation strategy will be collected and examined

12 SAFETY

As the components of this study are all within the realm of usual clinical care and common clinical practice, we do not anticipate any incremental adverse events. Patients will report symptoms/adverse events to their local site study coordinator and primary cardiac electrophysiologist during the follow-up period. The local site primary investigator will oversee the safety of the study at his/her site. All adverse events will be reported to the Principal Investigators (Drs. Aryana and d'Avila). Adverse events will be monitored and tallied for each 10 patients enrolled in the study.

13 RISK

As the protocol described is standard to an AFp ablation procedure, the risks of the procedure are similar to that of a standard AF procedure[19] and include:

Common:

- Discomfort at the site of venous access
- Groin hematoma

Uncommon:

- Cardiac Perforation requiring drainage or surgery
- Pulmonary venous stenosis/occlusion
- Thrombus formation/stroke

- Injury to adjacent structures (phrenic nerve, esophagus, lung, cardiac valves)
- Bleeding
- Congestive heart failure
- Renal dysfunction
- Vascular complications (pseudoaneurysm, AV fistula requiring surgical intervention)
- Myocardial infarction
- Transesophageal echocardiography risks include dental and esophageal injury
- Radiation burns
- Pneumonia and/or sepsis
- Anaphylaxis
- Death

14 DATA HANDLING

Information about registry patients will be kept confidential and managed according to the requirements of the United States of American Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed patient authorization informing the patient of the following:

1. What protected health information (PHI) will be collected from patients
2. Who will have access to that information and why
3. Who will use or disclose that information
4. The rights of a research patient to revoke their authorization for use of their PHI

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the patient is alive) at the end of their scheduled registry period. In order to ensure patient confidentiality, all CRFs and patient information (NavX study DVDs, and ambulatory ECG monitors, CT/MR, echocardiograms if reviewed) will be de-identified and replaced with a unique three-digit patient identifier. Information will be stored in the office of the local study coordinator which will be locked when he/she is not in the office. The research study

coordinators, principal investigator and co-investigators will be the only people with access to this data. All data will be stored without any patient information apart from the unique three digit patient identifier. There will be a code sheet that will link the de-identified data back to the subjects. This will be encrypted and password-protected. One copy will be stored in the primary investigator's computer, and another in the research coordinator's computer.

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