Prophylactic Limited Left Sided Maze Procedure to Prevent Post-Operative Atrial Fibrillation in Adult Cardiac Surgery Patients

(PREVENT AF-Feasibility Study)

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Objective

To evaluate the safety and effectiveness of a prophylactic limited left sided maze procedure in subjects undergoing cardiac surgery to decrease the incidence of post-operative atrial fibrillation (POAF).

Background

Atrial fibrillation (AF) is the most common complication following adult open heart surgery and is the leading cause for prolonged hospital stay (1,2). The incidence of this common post-operative complication is 30 to 60% (1,25). POAF places enormous strain on hospital resources and subjects' immediate post-operative wellbeing. More importantly, patients who experience POAF have decreased long-term survival (33,34). Currently there is no effective treatment to prevent POAF (25,26). Although multiple preventative therapies have been trialed the overall incidence remains at around 40% (Society of Thoracic Surgeons Database 2017). New treatment strategies are needed to reduce or eliminate the occurrence of POAF. An effective strategy would lessen the associated morbidities such as hypotension and heart failure, exclude the additional medications especially anticoagulants, and negate the added hospital length of stay (LOS) incurred by this complication.

AF is an abnormal and irregular heart rhythm in which electrical signals are generated chaotically throughout the upper chambers (atria) of the heart. Studies have demonstrated increased risk factors for the development of POAF (11,12,15). The predominant risk factor is age. Age 70 or greater predicts a minimum 30% risk of POAF with isolated coronary artery bypass grafting (CABG) surgery (11,12,15,18). An isolated aortic valve replacement (AVR) in this age group carries a 40% risk while a combined AVR/CABG, MVR (mitral valve replacement)/CABG or AVR/MVR have a 60% risk of POAF (18,25). Although there are other published risk factors which increase the occurrence of POAF such as low ejection fraction, peripheral arterial disease, diabetes, chronic obstructive pulmonary disease, or renal failure; they are not consistent throughout the literature (11,12,15,18).

The economic impact of POAF on hospital resources is staggering. POAF lengthens hospital stay an average of two to four days costing the health care system an estimated 2 billion dollars per year (1,3). Additionally, there are associated costs and morbidity such as bradydysrhythmias, hypotension,

bleeding, and the utilization of antiarrhythmic and anticoagulant drugs in the treatment of POAF. The most severe complication of POAF is stroke and patients permanently debilitated by a stroke are known to have a decreased life expectancy (4,9).

Ninety percent of thrombi resulting from AF are found in the left atrial appendage (LAA) and are thus the source of embolic stroke due to AF (20). Post open heart surgery patients who experience POAF are at nearly a 20% risk for long term AF with all its adverse sequela including heart failure and decreased survival (22).

Although multiple causes for POAF have been examined such as inflammatory mediators, autonomic innervation, or surgical trauma, one definitive etiology has not been found (1,25). What is known is that the etiologic cause stimulates firing of the most common (90%) triggers of AF which are electrical impulses originating in the pulmonary veins (10). The procedure to eliminate these drivers of spontaneous electrical activity causing AF is known as ablation. Ablation can be done in the cardiac catheterization lab or the operating room. Different energy sources such as cryotherapy, radiofrequency, or high intensity ultrasound, may be used depending on operator preference. Whether performed surgically or percutaneously the cornerstone of ablative therapy relies on pulmonary vein isolation (35,36). Ablation has been proven to be more effective than medical therapy regardless as to the context in which AF occurs (35,36).

Many studies have been done to evaluate medical interventions to prevent POAF and recommendations by the American College of Cardiology and Heart Rhythm Society are available to clinicians. The first line (Class Ia) and probably most effective therapy is beta blockers. Studies promoting amiodarone, the second most common recommended treatment (Class IIa) to prevent POAF, have not shown better than a 15-20% decrease in the incidence of POAF (38,39). Using beta blockers and amiodarone in combination also has been shown to reduce the incidence of POAF however there are marked side effects and drug interactions with the routine use of amiodarone. None of these trials have been able to demonstrate better than a 20% reduction in POAF (1,37,38). Specifically, two of the largest and most cited are the BLOSS trial for beta blockers and the ARCH trial for amiodarone which current medical therapy is based on (46,47). Of major significance is in spite of mandatory perioperative beta blockers for all CABG patients in the United States, the POAF incidence remains around 30% (45). Sotalol has also shown some partial benefit in reducing POAF however it is no longer on formulary at Spectrum Health Hospital due to its toxic side effects.

AtriCure is a medical device company that manufactures an FDA approved synergy ablation system consisting of the Ablation and Sensing Unit(ASU2), an AtriCure Switch box(ASB3), an AtriCure® Synergy Ablation Clamp, and a footswitch. When activated, the ASU2 delivers radiofrequency energy to the linear electrodes on the insulated jaws of the Synergy Ablation Clamp. The AtriCure® Synergy Ablation Clamp is a single patient use electrosurgical instrument designed to ablate cardiac tissue for the treatment of patients with atrial fibrillation who are undergoing concomitant cardiac surgery (Figure 1). The clamp uses two pairs of radiofrequency electrodes to deliver transmural lesions on the myocardium. The ASU2 is activated by depressing the footswitch. Once activated, the ASU2 emits a continuous audible tone. This tone confirms that current is flowing between the jaws of the Synergy Ablation Clamp. When the tone turns to intermittent, tissue impedance has been achieved and the footswitch can be released (IFU).

The AtriCure® Synergy Ablation System measures tissue impedance and temperature throughout the ablation cycle and uses this information to control the application of energy to the tissue. The amount of energy delivered to the tissue is driven solely by tissue impedance. The System determines the minimum energy delivery required to create a transmural (full thickness) lesion based on tissue impedance and delivers only that amount of energy to the tissue. The time to tissue impedance varies but has been shown to complete a transmural lesion at an average of 16 seconds. (41) Energy delivery changes throughout the ablation cycle as tissue impedance changes. The lesion is visible as a white coloration of the tissue. The device is designed such that the lesions will not spread beyond the jaw width (IFU).

The efficacy of this device in creating a transmural scar to block the abnormal impulses from the pulmonary veins has been proven in the ABLATE trial and animal studies (27,41).

The AtriCure device is FDA approved for both the surgical treatment of AF and the ablation of cardiac tissue.

Figure 1

The limited left sided surgical maze procedure involves amputation of the left atrial appendage (LAA) and the creation of bilateral lesions encircling the outside of the left atrium just proximal to the entrance of the pulmonary veins (Figure 2). The effectiveness of the limited left sided surgical maze in restoring and maintaining sinus rhythm in the literature is 90% at one year (6,13,31). At Spectrum Health utilizing the Atricure in both chronic and paroxysmal AF our 30 day success rate is 74%. A limited left sided surgical maze procedure, as opposed to a full left or bi-atrial maze, does not require opening the cardiac chambers to create additional lesions inside the left or right atrium. Whether performing a limited or full left sided surgical maze procedure, when it is done concomitantly with the primary cardiac operation, no additional risks are incurred by the patient (7,8,28).

Amputation of the LAA is common practice amongst some cardiac surgeons to decrease the risk of stroke. It is a routine part of the maze procedure as it has clearly been shown to decrease the risk of stroke, without added risk for bleeding, as well as eliminating myocardium with a possible trigger of AF (10,20,29). A prospective, randomized trial from the University of Copenhagen presented at the 2017

European Society of Cardiology conclusively demonstrated that surgical occlusion of the LAA markedly decreased the risk of stroke in comparison to controls: at 3.7 years 6% in patients with no LAA versus 18% in the control population(42).

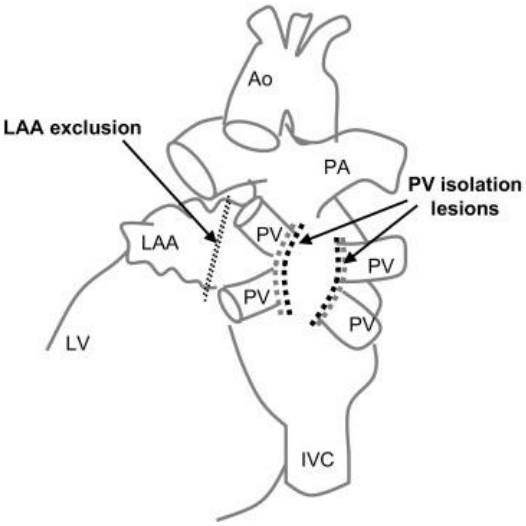

Figure 2. Pulmonary vein isolation procedure

Hypothesis

We hypothesize that performing a prophylactic limited left sided surgical maze, i.e., pulmonary vein isolation and excision of the left atrial appendage, in a group of at risk cardiac surgical patients at the time of the index procedure, will reduce the incidence of POAF. The null hypothesis is that the prophylactic surgical ablation will have no effect on the incidence of POAF.

Setting of the Research

This study will be conducted at a single center, Spectrum Health. The PI and all Spectrum Health cardiothoracic surgeons participating in the study are highly qualified and certified by the American Board of Thoracic Surgery. They are all proficient in performing the maze procedure as it is commonly utilized in everyday practice to manage and treat AF.

Subjects will be seen in the cardiothoracic surgeon's office and/or the hospital inpatient setting. The surgery will be performed at the Meijer Heart Center, Spectrum Health Hospitals.

Resources Available to Conduct this Research

Spectrum Health cardiothoracic surgeons perform approximately 1200 heart surgeries per year. Approximately 300 of these surgeries which include isolated coronary artery bypass grafting (CABG), isolated aortic valve replacement (AVR), or combined AVR/CABG are performed in patients ≥ 70 years of age. Therefore, we do not anticipate difficulty recruiting the necessary number of subjects during the enrollment period.

The PI will have dedicated research time in his schedule. Experienced research staff from the CV Structural Heart Team will assist with the study as delegated by the PI**.**

Study Design

This is a single-center, prospective, randomized, unblinded, interventional feasibility study to determine whether or not a prophylactic limited left sided surgical maze procedure is effective in reducing or preventing POAF. A high risk population with no history of atrial fibrillation or flutter, with a baseline risk of POAF of 40% or greater will be chosen. This includes CABG/AVR, isolated AVR, and isolated CABG patients 70 years and older. Up to 60 subjects who are scheduled to undergo elective open heart surgery will be randomized 1:1 into one of two study arms:

1. Control arm: Elective open heart surgery without a limited left sided maze procedure.
2. Treatment arm: Elective open heart surgery with a limited left-sided maze procedure.

Sample Size Determination

No sample size calculation was performed as this is a feasibility trial and the number is fixed at 60 patients where 30 will be randomly assigned to the control arm and 30 randomly assigned to the treatment arm.

Statistical Methods

Summary statistics will be calculated. Quantitative variables will be expressed as mean ± standard deviation or median [interquartile range]. Qualitative variables will be expressed as frequency (percent). To determine if there is an association in POAF and the two arms of the study, a Chi-Square Test or Fishers Exact test will be used depending on assumptions being met. To look at our secondary outcomes such as hospital length of stay and incidence of postoperative reoperations for bleeding, a two sample t-test or Wilcoxon Rank Sum will be used to determine if there is a difference between the two groups and those that had POAF vs. those that didn't. Significance will be assessed at the 0.10 level. A level of 0.10 will provide more power to the study while only allowing a slight increase in error.

Recruitment methods

All subjects who receive an inpatient or outpatient heart surgery consult and meet the criteria may be approached about study participation. Consults will occur in the Cardiothoracic Surgeon's office of the Meijer Heart Center or Spectrum Health inpatient units. The subject's electronic medical records (EMR), Cerner and Epic, will be reviewed. There are no plans for advertisement or patient payment related to study participation.

It is expected enrollment will take approximately 6 months.

Inclusion and Exclusion criteria

Inclusion Criteria

1. Male or female
2. Age ≥ 70 years
3. Elective cardiac surgery: isolated AVR, isolated CABG, or AVR/CABG,

Exclusion Criteria

1. A history of AF or atrial flutter
2. Less common cardiac operations such as aortic root replacements, aortic dissections, myxoma excisions, or pericardectomies. Beating heart or off-pump procedures, redo open heart procedures.
3. Subjects with existing pacemaker and/or AICD
4. Vulnerable populations; adults unable to sign consent, prisoners
5. Need for emergent or salvage surgery for any reason
6. Currently participating in an investigational drug or another device study (excluding registries)
7. Subjects currently on antiarrhythmic drugs Class I and III including amiodarone.

Study endpoints

The incidence or absence of documented AF, defined by Society of Thoracic Surgeons (STS) registry data as the occurrence of POAF or atrial flutter that requires treatment, is the primary endpoint (21). In addition, length of stay (LOS) and additional antiarrhythmic or anticoagulant medications will be examined as a secondary endpoint.

Safety endpoints

The safety endpoint is the occurrence of one of the following events between time of procedure and the 30 day post procedure assessment:

- All-cause death
- TIA/stroke
- Bleeding (chest tube drainage) that is procedure related and requires take back to the operating room or blood transfusions
- Incidence of AF
- Need for permanent pacemaker
- Evidence of pulmonary vein stenosis defined as > 50 % occlusion of the vessel.

Procedures Involved in the Research

Baseline preoperative cardiac surgery workup will be done on all patients according to standard of care. This workup will consist of:

- History and physical exam
- Chest X-Ray

- Electrocardiogram
- Echocardiogram
- Cardiac catheterization
- Blood and urine tests such as complete blood count, complete metabolic count, cardiac enzymes, type and screen, and urinalysis. Any other indicated tests based on patient history and index procedure i.e.; pulmonary function tests, carotid ultrasound, leg vein mapping, noncontrast chest CT.

Prior to enrollment, the protocol and informed consent must be approved by the Spectrum Health Institutional Review Board (IRB). IRB approved Health Insurance Portability and Accountability Act (HIPPA) will also be used. A regulatory binder and subject binders will be created according to local requirements and stored in the CV Research Department.

Before the subject signs the informed consent form (ICF), the investigator or designated study personnel will explain the research, study procedure, anticipated benefits, and potential risks of study participation. Adequate time will be allowed to read the ICF and ask questions. The original signed ICF will be kept with the subject's research records and a copy will be given to the subject.

All subjects will be on a beta-blocker preoperatively and throughout the hospitalization as per STS guidelines unless there is a clear contraindication. The use of amiodarone or other antiarrhythmic agents for prevention of POAF are not allowed. Should a patient experience POAF standard treatment with amiodarone or other agents may be utilized.

A 1:1 randomization will occur prior to surgery using REDCap to allocate subjects into the treatment (planned open heart surgery plus limited left-sided maze) or control arm (planned open heart surgery). The subject will be notified of their randomization assignment.

Care on the morning of surgery will follow current standards of care. Baseline vital signs will be obtained and the subject will be placed on telemetry. Vital signs such as blood pressure, heart rate and rhythm, central venous pressure, oxygen saturation will be monitored throughout the case as per standard of care.

After establishing cardiopulmonary bypass and myocardial arrest for the primary heart surgery procedure, the limited left sided surgical maze procedure will be performed on those patients who were randomized to the treatment arm of the study. An encircling lesion will be performed around the left atrial tissue just proximal to the entrance of both the left and right pulmonary veins utilizing the AtriCure® Synergy Ablation System according to Instructions for Use (IFU). The targeted tissue of the pulmonary vein will be placed between the distal and proximal jaws of the synergy ablation clamp ensuring that no tissue extends beyond the indicator line or into the jaw heel. The ASU2 is activated by pushing the footswitch. Once activated, the ASU2 emits a continuous audible tone indicating that current is flowing between the jaws of the clamp. When the tone turns to intermittent, it indicates tissue impedance has been met and the transmural lesion completed, then the footswitch is released. The system determines the minimum energy delivery needed to create a transmural lesion. This is based on tissue impedance and only that amount of energy will be delivered to the tissue (IFU). Time

needed to create a transmural lesion varies according to tissue thickness, composition, and the length of tissue within the clamp but averages 16 seconds (41).

No deviation from the IFU will occur, nor will the device be altered in any way.

The synergy ablation clamp is connected to a monitor screen with a digital graph to display the conduction over time of the myocardial tissue clamped between the device jaws. It is the transmural scar which develops that prevents the abnormal impulses from the pulmonary veins from communicating with the myocardial electrical system.

The efficacy of the AtriCure clamp in creating complete circumferential lesions has been demonstrated in animal studies and the RESTORE SR and ABLATE trials. Because the efficacy of the technology to ensure transmural lesions has been proven, entrance and exit block are not checked by most surgeons and neither is it our practice at Spectrum Health. Further the FDA approval and instructions for use of the Atricure device do not require the confirmation of entrance or exit block.

Our current surgical ablation success rate at Spectrum Health in treating patients ≥ 70 years old with both chronic and paroxysmal AF is 74% at 30 days.

Amputation of the LAA will involve transecting the appendage at its base ensuring that all of the appendage tissue is removed. The wound will be closed with a continuous double layer of 4-0 Prolene suture. The site will be carefully inspected to ensure complete wound closure and no signs of bleeding. All surgeons will utilize the same method for LAA amputation.

The four pulmonary veins are large blood vessels that receive oxygenated blood from the lungs and drain into the left atrium of the heart. (Figure 3)

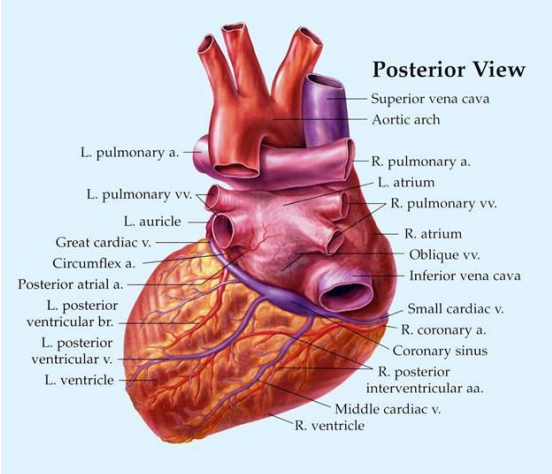

Figure 3

This FDA approved device is currently in use and is well known to the surgeons participating in this study, thus no additional training or instruction will be required. Because this is a limited left sided surgical maze procedure, limited to the epicardium, the left atrium will not require entry.

After completion of the limited left sided surgical maze procedure, for those patients who were randomized to the treatment arm, the remainder of the elective heart surgery will proceed. Patients who were randomized to the control arm will proceed directly to their index cardiac surgery and will not have either component of the surgical maze procedure.

Postoperative monitoring, diagnostic and lab tests will be done according to Spectrum Health standard of care. Current standard of care for the postoperative cardiac surgery patient at this institution consists of continuous telemetry monitoring, collection of arterial blood gases, complete blood count, basic metabolic panel and blood glucose at regular intervals. An EKG is obtained on arrival to the recovery area and any time a cardiac dysrhythmia is noted.

In addition to standard of care, subjects who were randomized to the treatment arm of the study will have a pre-discharge transthoracic echocardiogram to assess the absence or presence of thrombus in the left atrium. If thrombi are noted, subjects will be anticoagulated per standard of care.

The highest risk of POAF is within the first 48 to 96 hours after surgery. All post-operative patients are on continuous 24 hour telemetry after surgery until hospital discharge. While it depends on the index procedure that was done, the usual length of stay at this institution following elective cardiac surgery is 5 to 7 days.

If subjects develop POAF, paroxysmal or sustained, they will be treated with standard medications and protocols already in place for this complication.

The current protocol to treat POAF first entails escalation of beta blocker therapy if it is tolerated. If further treatment is necessary, patients are loaded with a dose of IV amiodarone and then changed to oral amiodarone for four weeks or longer if appropriate.

Our current standard of care at Spectrum Health for POAF anticoagulation is as follows. For POAF that persists for more than 24 hours or is episodic and occurs more than once, anticoagulation is initiated. Warfarin or one of the new oral anticoagulants such as dabigatran, rivaroxaban or apixiban will be used tailored to the individual patient utilizing their CHA2DS2-VASc score and surgeon preference.

In addition, all patients who receive a mechanical valve or a bio prosthetic mitral valve are started on an anticoagulant on postoperative day 2. The dose is titrated to an INR of 2.5-3.5.

To our knowledge isolated radiofrequency epicardial pulmonary vein lesions have not resulted in endocardial thrombus. Nor has this been reported with the AtriCure clamp. The current recommendations are to anticoagulate patients who undergo surgical ablation with endocardial lesions or full surgical Maze procedures which involve additional lesions in the left and/or right atrium (35,36). At Spectrum Health we perform 1200 open heart surgery procedures per year and it is not our standard to anticoagulate patients after isolated PVI who remain in sinus rhythm except for a daily aspirin. Of note all cardiac surgical patients are on daily Lovenox postoperatively to prevent deep venous thrombosis.

Subjects will be visited daily by research staff during the index hospitalization. The EMR will be reviewed with a focus on any episodes of POAF or any other cardiac dysrhythmias, any need for pacemaker, chest tube drainage or need for blood transfusion beyond what is normal for this patient population.

The initial follow-up for POAF occurrence will be 30 +/-7 days post hospital discharge; this is standard for post-operative surgical care. Additional follow-up, consisting of electronic medical record (EMR) review anywhere care is given, will occur at 6 weeks, 6 months and 12 months post procedure. Review of subject data will include any adverse events that may have occurred, EKG, and echocardiogram review. If data is not available in the EMR, phone calls will be made to subjects.

Data management

Research Electronic Data Capture (REDCap) will be used for randomization and data collection. REDCap is password protected and only IRB study approved personnel will have access to the data.

Standard practice is to enter this group of surgical patient's information into the Society of Thoracic Surgeons (STS) Registry. Subjects in this study will be included in the STS Registry.

Data to be collected will include:

- Subject name, date of birth and medical record number
- Gender, age
- Inclusion/Exclusion criteria
- Medical History: hypertension (HTN), diabetes mellitus (DM), hypercholesterolemia, chronic lung disease, peripheral vascular disease (PVD), coronary artery disease (CAD), CHF, chronic kidney disease (CKD), cerebrovascular disease (stroke/TIA)
- Echocardiogram (pre-op and pre-discharge (treatment arm only)): EF, LA measurement, LV measurement, mitral regurgitation, tricuspid regurgitation
- Medications, pre- and post-op including name of medication, indication, dose.
- Procedure and date- including number of grafts and type of valve implanted
- CPB time, X-clamp time
- EKG rhythm(s), pre- and post-op (atrial flutter, SVT, VT, etc.)
- Post procedural stroke/TIA
- Post procedural MI
- Post procedural pacemaker implant
- Any bleeding complication
- Any incidents of POAF (date occurred, treatment used,)
- Length of stay

Data will also be collected at 6 weeks, 6 months and 12 months post-procedure. This will include:

- All adverse events
- Any rehospitalizations
- Medications, current and new
- Any episodes of AF or other cardiac arrhythmias
- EKG
- Need for pacemaker

- Echocardiogram: EF, valve gradients, left and right atrial function, pulmonary vein stenosis or presence of suspected thrombus.

In the event that we are unable to find subject information in the EMR at appointed study intervals, we may telephone subjects to inquire how they are and whether or not they have had any adverse events.

Assessments/procedures	Baseline	Hospitalization	Predischarge	Follow up	Follow up	Follow up
	Screening			6 weeks post procedure +/-7 days	6 months post procedure +/- 7 days	12 months post procedure +/- 7 days
Consent	X					
History/Inclusion and Exclusion	X					
Medication Review	X	X		X	X	X
Randomization	X					
AF occurrence and treatment		X		X	X	X
Transthoracic echo			X Treatment arm only			
Rehospitalizations				X	X	X
Adverse Events		X		X	X	X

Adverse events

An adverse event (AE) is any untoward medical occurrence (signs, symptoms, abnormal laboratory findings) in a subject. It does not necessarily have to be caused by the device or procedure to be considered an adverse event.

A serious adverse event is one that led to death, serious deterioration in the health of the subject, resulted in a new hospitalization or prolonging the index hospitalization, a permanent impairment of a body structure or function, or required medical and/or surgical intervention to prevent further life-threatening illness or injury

A device related adverse event is an event that in the investigators judgement may be related to the investigational device.

Adverse events reporting will include the categories of cardiac, respiratory, vascular, bleeding, neurological (stroke/TIA), other organ complications and infection. Adverse events will be monitored by research staff and the investigator from the time of cardiac surgery until 365 days post procedure. AEs will be categorized according to seriousness and device and/or procedure relatedness. The monitoring of adverse events will occur from the time of cardiac surgery, throughout the hospitalization, at the 30 day, 6 week +/- 7 days, 6 months +/- 7 days and 12 months +/- 7 days post procedure assessments.

Serious adverse events or serious adverse device-related events will be reported to the FDA and Spectrum Health IRB per the regulations and reporting procedures.

If any thromboembolic events are observed during the study, an adverse event form will be submitted to the FDA. This report will include anonymized information on the procedure, type, and severity of thromboembolic event, the patient specific anticoagulation protocol, and the total number of subjects enrolled and treated in each arm by the event time.

Adverse events will be reported and recorded in REDCap and will include the following information:

- Date of onset first observation
- Description of event
- Seriousness of event
- Causal relationship to device/procedure
- Treatment required
- Outcome/resolution

The investigator and the non-study cardiothoracic surgeon will review all AEs.

For the purposes of this study certain events will be considered part of the expected post-operative course and will not be reported unless the investigator feels they deviate from the norm:

- Post-operative pain requiring medication
- Temporary mental status changes (except TIA/stroke)
- Mild GI disturbances, i.e. decreased appetite, nausea, vomiting, constipation or diarrhea
- Respiratory findings post-surgery, including oxygen usage, pleural effusion, atelectasis
- Minor laboratory findings, including hypokalemia, hyperkalemia, hypocalcemia, hypomagnesemia, leukocytosis, thrombocytopenia, hyperglycemia
- Post-operative anemia d/t intraoperative blood loss/dilution requiring $\leq$ 2 U transfusion
- Low-grade fever < 38.5◦ C
- Hypo/hypertension requiring treatment
- Mild creatinine increase, $\leq$ 0.3 mg/dL

Provisions to Monitor the Data for the Safety of Subjects

Data will be reviewed by a non-study cardiothoracic surgeon; John C. Heiser, MD. The review will include subject eligibility, documentation of the consent process, adverse events, and subject withdrawals. Review will occur after every 5 patients have a completed surgical procedure and are discharged from the hospital. Adverse Events (AE) will be evaluated for seriousness, unanticipated, procedural and/or device-relatedness. If any Serious Adverse Events (SAE) occur beyond what is expected in this patient population and are thought to be related to the limited left sided surgical maze procedure, the FDA and Spectrum Health IRB will be notified per reporting practices and the study may be terminated.

Monitoring of patient data will continue throughout the study at the scheduled assessment times.

Withdrawal of subjects

We do not foresee any circumstances in which subjects would want to withdraw from the study. However, subjects may withdraw from this study at any point, it will not be held against them nor involve penalty or loss of benefits to which subjects are otherwise entitled.

Risks/Benefits to Subjects

Neither LAA amputation or pulmonary vein isolation ablation, the 2 components of the limited left sided surgical maze procedure, have been shown to pose additional risk to the subject over the primary open heart procedure (7,8,16,28).

Potential adverse events with this combined procedure are similar to the risks of cardiac surgery and are listed below as described in the AtriCure® Synergy Ablation System Instructions for Use:

- Death
- Excessive bleeding that may require re-intervention
- Cardiac tamponade
- Pulmonary vein stenosis
- Restrictive or constrictive pericarditis
- Infection that may result in sepsis or endocarditis
- Myocardial infarction (MI)
- Stroke or transient ischemic attack (TIA)
- Thromboembolism
- Diaphragmatic (phrenic nerve) paralysis
- Esophageal-left atrial fistula or esophageal rupture
- Atrial perforation or rupture
- Ventricular perforation or rupture
- Atelectasis
- Pneumonia
- Congestive heart failure
- Cardiac valve injury
- Persistent pneumothorax
- Excessive pain and discomfort
- Deep sternal wound infection (mediastinitis)
- Perioperative atrial or ventricular rhythm/conduction disturbance
- Pericardial effusion
- Injury to the great vessels
- Injury to unintended surrounding tissues, including tears and punctures
- Extension of cardiopulmonary bypass time or aortic cross clamp time

Potential risks already listed above that may be associated with the limited left sided surgical maze procedure include:

- Additional time on Cardiopulmonary Bypass Pump
- Additional ventilation and anesthesia
- Pulmonary vein stenosis
- Need for permanent pacemaker
- Bleeding
- Unintentional damage to tissue near the pulmonary vein
- Atrial flutter

The AtriCure® Synergy Ablation System is FDA approved and utilized around the world by cardiothoracic surgeons to treat AF. In the United States, it is the preferred device of surgeons to treat AF and is used approximately 200-250 times a year at Spectrum Health to perform concomitant maze procedures. The cardiothoracic surgeons at Spectrum Health are familiar with the AtriCure® Synergy Ablation System and technically capable of performing the maze procedure. Thus a proven device, along with a known common procedure, i.e., pulmonary vein isolation and LAA amputation, will be studied in an expanded population of patients, those without a history of AF, who are already undergoing open heart surgery.

Paramount to this investigation is patient safety and the risk-benefit ratio incurred by the patient. Neither LAA amputation nor pulmonary vein isolation has been shown to pose additional risk to the patient beyond the primary operation (7,8,16,28,44). Although the potential risk list as stated above is extensive, the list is inclusive of risks common to all adult open heart procedures and can be associated at the time of surgery with the risk of a maze procedure.

There have been no documented cases of pulmonary vein stenosis, defined as > 50% vessel occlusion, as the lesion is created on the left atrial cuff proximal to the entrance of the pulmonary veins (23), nor is there any risk of phrenic nerve injury as the lesion is well away from the nerve.

In regard to postoperative atrial flutter after a surgical maze, the risk is extremely low. With pulmonary vein isolation alone by radiofrequency, atrial flutter has not been quantified. There are rare sporadic case reports after a full maze (24). If atrial flutter is not amenable to medical management patients may require a catheter based ablation by an electrophysiologist.

There have been reports that amputation of the LAA may increase the risk of POAF but these are not consistent and a recent meta-analysis demonstrated no increased risk of POAF (43). Further a surgical Cox maze is always defined by management of the LAA either with amputation or creation of an epicardial surgical lesion at its base and occlusion of the LAA. Long term results of the maze procedure show no ill effects to the patient and left atrial transport function is maintained (30).

Globally the AtriCure device has been safely used in over 200,000 cases and is the predominant device used to perform surgical ablation of AF in the world. Thus the safety of the AtriCure device has been outstanding with almost no risk to the patient and the ablation lesions have no late or long-term adverse effects on the myocardium.

In a study published in Circulation of over 10,000 patients who underwent amputation of the LAA there was no increased risk of bleeding (16). Multiple large studies have demonstrated that a left sided or limited left sided surgical maze procedure adds no operative risk and only improves patient outcomes, especially in regard to long term stroke risk and survival (7,8,17,28,29,44). A recent 2018 publication from the STS Adult Cardiac Database strongly corroborates LAA removal as it markedly decreased the long term risk of stroke (42).

The strongest evidence, that there is no additional risk to the patient, is put forth in the 2017 Guidelines for The Surgical Treatment of Atrial Fibrillation set by The Society of Thoracic Surgeons: "Surgical ablation for AF can be performed without additional operative risk, and is recommended at the time of concomitant isolated AVR, isolated CABG and AVR+CABG operations to restore sinus rhythm." The Society of Thoracic Surgeons labels this as a Class I recommendation; meaning that the procedure should be performed as a standard of practice because it is useful, effective, and the benefits far outweigh the risks.

A recent Russian study examining the effects of prophylactic pulmonary vein isolation with radiofrequency ablation in patients undergoing isolated CABG has shown very promising results. The incidence of POAF was reduced by 21% versus controls and at one year the effect was sustained as 98% of the prophylactic group was free from AF versus 84% of the controls. The conclusion was "simultaneous preventive pulmonary vein isolation during CABG is safe and effective"(40).

There are subsets of cardiac surgical patients where a prophylactic maze has already shown benefits because the risk of developing POAF is so high and the adverse sequela so morbid. It is recommended that a prophylactic maze be considered in the setting of re-operative open heart surgery patients with a dilated right or left atrium (19). A prophylactic maze is also warranted in the subset of patients who undergo a combined mitral valve and tricuspid valve operation even if they are in sinus rhythm (14).

If our hypothesis proves true, the benefits of a prophylactic limited left sided surgical maze procedure will impact thousands of cardiac surgical patients. At a minimum, those over age 70 have a 30% chance of developing POAF with any open heart surgical procedure (11,12,15,18). The detrimental effects of this complication include stroke, hemodynamic instability, additional medications for rate control and anticoagulation with their side effects, and prolonged length of hospital stay. Even if patients revert back to sinus rhythm they are discharged on additional medications to prevent recurrence and stroke. Anticoagulation alone for POAF carries a 3-4% annual risk of major hemorrhage (32). The 20% of patients who remain in POAF have a lifelong risk of increased stroke and decreased survival (9,20,22). Such risks are by far more serious than any risk posed by a prophylactic limited left sided surgical maze procedure which carries a risk of less than 1% for any complication. Thus should our strategy successfully reduce or eliminate the incidence of POAF, the immediate benefit to cardiac surgical patients will be immense and markedly decrease the burden on the health care system.

Provisions to Protect the Privacy Interests of Subjects

Explanation of the study and consenting will be done in a private area of Spectrum Health. HIPPA will be followed according to standard practice.

Confidentiality of Data

Only IRB approved research staff will have access to study data. Subject binders will be kept in a secure area of the CV Research office. REDCap will be utilized, the database is password protected. Data will be stored according to current policy and procedure.

Medical care and compensation for Injury

While not anticipated, if subjects are injured or made sick from taking part in this research, medical care will be provided. No funds have been set aside to pay subjects in the unlikely event of a research related injury.

Cost to Subjects

Application will be made to CMS for reimbursement consideration. Subject's health insurance will be billed for costs that are part of usual medical care. Any co-payment, co-insurance or deductible, will be the responsibility of the subject. There are no extra costs to subjects for participating in this research study. The pre-discharge transthoracic echocardiogram required for the study (treatment arm only) will not be billed to the subject or their insurance.

Consent Process

Once a subject has been identified as meeting criteria for the study, the PI and/or other delegated study personnel will explain the study in detail to the subject. This discussion will take place in privacy at Spectrum Health. Adequate time will be allowed for questions. A copy of the consent will be given to the subject to read and review. After allowing the subject adequate time to review the consent, the research coordinator will answer any additional questions and ensure that the subject realizes participation is voluntary. A signed copy of the informed consent will be given to the subject.

Sharing of Results with Subjects

There are no plans to share research results with subjects.

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