STUDY PROTOCOL

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Left Atrial Appendage Closure During Cardiac Surgery in Atrial Fibrillation Patients with Seralene®

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Principal Investigator:

Prof. Lazar Velicki, MD, PhD

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1.BACKGROUD AND RATIONALE

1.1. Background

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice, affecting millions of individuals worldwide. It significantly increases the risk of stroke, thromboembolism, and mortality. The left atrial appendage (LAA) is a small, pouch-like structure located in the left atrium of the heart. It serves as a reservoir for blood stasis and is a primary site for thrombus formation in patients with AF. Anticoagulation therapy, typically with oral anticoagulants such as warfarin or direct oral anticoagulants (DOACs), has been the cornerstone of stroke prevention in patients with AF. However, anticoagulation therapy is associated with bleeding complications, requires regular monitoring, and is contraindicated in some patients due to increased bleeding risk or other comorbidities. Left atrial appendage closure has emerged as a promising alternative strategy for stroke prevention in patients with AF. By occluding the LAA, the source of thrombus formation is eliminated, potentially reducing the risk of stroke while obviating the need for long-term anticoagulation therapy. Various percutaneous devices have been developed for LAA closure and have demonstrated efficacy in reducing stroke risk in select patient populations.In recent years, there has been increasing interest in performing LAA closure during cardiac surgery, particularly in patients undergoing procedures such as coronary artery bypass grafting (CABG) or valve surgery. This approach offers the advantage of addressing LAA closure concomitantly with the primary surgical intervention, potentially reducing procedural time and avoiding the need for additional invasive procedures. Additionally, the surgical approach may allow for more complete LAA exclusion compared to percutaneous techniques.

However, despite the potential benefits, the optimal method and timing of LAA closure during cardiac surgery remain areas of debate. Questions regarding the safety, efficacy, and long-term outcomes of LAA closure during cardiac surgery need to be addressed through rigorous clinical investigation. Randomized controlled trials comparing LAA closure during cardiac surgery to standard care, with appropriate follow-up for clinical endpoints such as stroke, bleeding complications, and mortality, are essential to inform clinical practice and guideline recommendations.

In light of the growing burden of AF and the need for effective stroke prevention strategies with fewer associated risks, investigating the role of LAA closure during cardiac surgery represents a critical area of research that has the potential to significantly impact patient outcomes and healthcare delivery.

1.2. Rationale

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia worldwide, affecting millions of individuals and significantly increasing the risk of stroke, thromboembolism, and mortality. The left atrial appendage (LAA) serves as a primary site for thrombus formation in patients with AF, contributing to the heightened risk of stroke. While anticoagulation therapy has traditionally been the mainstay for stroke prevention in AF, it is associated with bleeding complications, requires regular monitoring, and is contraindicated in some patients.

Given the limitations and risks associated with anticoagulation therapy, there has been growing interest in alternative stroke prevention strategies, such as LAA closure. LAA closure aims to eliminate the source of thrombus formation, thereby reducing the risk of stroke while potentially obviating the need for long-term anticoagulation therapy. While percutaneous LAA closure devices have shown promise in reducing stroke risk in select patient populations, there remain questions about the optimal method and timing of LAA closure, particularly in patients undergoing cardiac surgery.

Performing LAA closure during cardiac surgery offers several potential advantages. First, it allows for concomitant treatment of LAA closure with the primary surgical intervention, potentially reducing procedural time and avoiding the need for additional invasive procedures. Second, the surgical approach may enable more complete LAA exclusion compared to percutaneous techniques, thereby potentially enhancing efficacy. Third, for patients already scheduled to undergo cardiac surgery for indications such as coronary artery disease, valve disease, or other structural heart diseases, the addition of LAA closure may offer a comprehensive approach to managing AF and reducing stroke risk in a single procedure.

Despite the theoretical advantages of LAA closure during cardiac surgery, there remains a paucity of robust clinical evidence to support its widespread adoption. Existing studies have reported variable efficacy rates and complication rates, and there is a lack of consensus regarding patient selection criteria, procedural techniques, and long-term outcomes. Therefore, there is a compelling need for well-designed, randomized controlled trials to rigorously evaluate the safety, efficacy, and long-term outcomes of LAA closure during cardiac surgery compared to standard care.

Such a study would provide valuable insights into the role of LAA closure as a stroke prevention strategy in patients with AF undergoing cardiac surgery. By systematically assessing clinical outcomes, including stroke, bleeding complications, mortality, and quality of life, this study could inform clinical practice and guideline recommendations, ultimately improving patient care and outcomes in this high-risk population.

2. RISK/BENEFIT ASSESSMENT

2.1. Known potential benefits

1. **Reduction in Stroke Risk:**
    - **Benefit:** LAA closure aims to eliminate the source of thrombus formation in patients with AF, thereby reducing the risk of stroke.

    - **Statistics:** Studies have reported significant reductions in stroke risk following LAA closure, with relative risk reductions ranging from approximately 30% to 70% compared to standard therapy, such as anticoagulation.

2. **Decreased Need for Anticoagulation:**
    - **Benefit:** Successful LAA closure may reduce the need for long-term anticoagulation therapy, thereby potentially lowering the risk of bleeding complications associated with anticoagulants.
    - **Statistics:** While specific statistics on the reduction in anticoagulation use following LAA closure vary, studies have reported a significant proportion of patients discontinuing or reducing anticoagulation post-procedure.

3. **Improved Quality of Life:**
    - **Benefit:** By reducing the risk of stroke and decreasing the burden of anticoagulation therapy, LAA closure may lead to improvements in patients' quality of life, including decreased anxiety related to stroke risk and freedom from anticoagulation-related side effects.
    - **Statistics:** Quality of life assessments using standardized questionnaires, such as the SF-36, have demonstrated improvements in various domains following successful LAA closure procedures.

4. **Procedural Feasibility and Safety:**
    - **Benefit:** LAA closure during cardiac surgery offers the advantage of concomitant treatment with the primary surgical intervention, potentially reducing procedural time and avoiding the need for additional invasive procedures.
    - **Statistics:** Studies have reported procedural success rates of LAA closure during cardiac surgery exceeding 90%, with low rates of procedural complications such as bleeding and device-related issues.

5. **Long-Term Efficacy:**
    - **Benefit:** Successful LAA closure during cardiac surgery may provide sustained protection against stroke over the long term, potentially reducing the need for ongoing stroke prevention therapies.
    - **Statistics:** Long-term follow-up data from studies on LAA closure, including those conducted during cardiac surgery, have demonstrated sustained efficacy in stroke prevention and low rates of device-related complications over time.

These potential benefits highlight the rationale for conducting a randomized controlled trial to further evaluate the efficacy, safety, and long-term outcomes of LAA closure during cardiac

surgery in patients with AF. Such a trial would provide valuable evidence to inform clinical practice and guideline recommendations regarding the management of stroke risk in this high-risk population.

2.2. Known potential risks

1. **Bleeding Complications:**
    - **Risk:** Bleeding complications, including intraoperative bleeding, postoperative bleeding requiring transfusion, and hematomas, are potential risks associated with cardiac surgery, including LAA closure.
    - **Statistics:** Reported rates of major bleeding events range from 1% to 5% in studies evaluating LAA closure during cardiac surgery.

2. **Pericardial Effusion and Tamponade:**
    - **Risk:** Pericardial effusion and cardiac tamponade can occur as a result of surgical trauma during LAA closure, leading to hemodynamic compromise and potentially requiring urgent intervention.
    - **Statistics:** Reported rates of pericardial effusion and tamponade vary but generally range from 1% to 3% in studies of cardiac surgery, including those incorporating LAA closure.

3. **Device-Related Complications:**
    - **Risk:** Device-related complications such as device embolization, device thrombosis, and device malposition are potential risks associated with LAA closure devices.
    - **Statistics:** Studies have reported device-related complication rates of less than 1% for LAA closure devices used during cardiac surgery. However, the specific rates may vary depending on the type of device and operator experience.

4. **Stroke and Thromboembolism:**
    - **Risk:** Despite the intention to reduce stroke risk, there is a potential risk of thromboembolic events associated with LAA closure, particularly in the perioperative period.
    - **Statistics:** Reported rates of stroke and thromboembolism following LAA closure during cardiac surgery are generally low, ranging from 1% to 3% in studies with appropriate follow-up periods.

5. **Infection:**
    - **Risk:** Surgical site infection or device-related infection is a potential risk following LAA closure during cardiac surgery.
    - **Statistics:** Reported rates of infection vary but are generally less than 1% in studies of cardiac surgery incorporating LAA closure.

It is important to note that the specific risks and their associated statistics may vary depending on factors such as patient characteristics, operator experience, procedural techniques, and the type of LAA closure device used. Additionally, these statistics are based on available evidence as of the time of writing and may evolve as more data become available from ongoing research

and clinical practice. Conducting a study on LAA closure during cardiac surgery will provide further insights into the risks and benefits of this intervention in the context of contemporary clinical practice.

3. DEVICE DESCRIPTION AND OPERATIVE TECHNIQUE

3.1.Device descritpion

The intervention consists of epicardial surgical closure of the left atrial appendage using the AtriLASH™ Left Atrial Appendage Closure System, a CE-marked, suture-based device utilizing SERALENE® material. The device is applied intraoperatively during cardiac surgery.

3.2. Operative technique

LAA closure with the Seralene® Loop would be conducted on the arrested heart during concomitant procedure at the time chosen by the operating surgeon. At the end of the procedure the closure would be double checked on transoesophageal echocardiography.

Successful procedure would include confirmation of no patency of the LAA followed by the length of stump <1 cm on transoesophageal echocardiography at the end of the procedure.

4. PROTOCOL SUMMARY

4.1. Clinical Trial Protocol Synopsis

Background: Left atrial appendage (LAA) closure has emerged as a potential strategy for stroke prevention in patients with atrial fibrillation (AF). While percutaneous LAA closure has shown promise, the role of LAA closure during cardiac surgery remains uncertain. The study aims to evaluate the safety and efficacy of LAA closure during cardiac surgery compared to standard care for stroke prevention in AF patients.

Study Design: multicenter, prospective observational study

Phase: The study would be physician initiated. Clinical in market study.

Description of sites enrolling participants : Four experienced cardiac surgical centers with over 1000 surgeries per year.

Description of study intervention: The Seralene® Loop (AtriLASH) would be applied for LAA closure during the concomitant cardiac surgical procedure during the cardioplegic arrest of the heart. The patency would be checked at the end of the procedure with transoesophageal echocardiography and successful procedure would include confirmation of no patency of the LAA followed by the length of stump <1 cm.

Follow up: Follow up exam would be done on 3 months postoperative by a cardiologist and transthoracic ultrasound exam will be performed to asses patency and stump length.

Additionally the exam and interview will assess any neurological complication in the follow up period.

Study Population: 200 patients. Patients aged 18 years or older with AF undergoing cardiac surgery with a CHA2DS2-VASc score ≥2 or equivalent stroke risk in addition to continued anticoagulation, scheduled to undergo cardiac surgery for indications such as coronary artery disease, valvular heart disease, or other structural heart diseases.

Study duration: 7-9 months

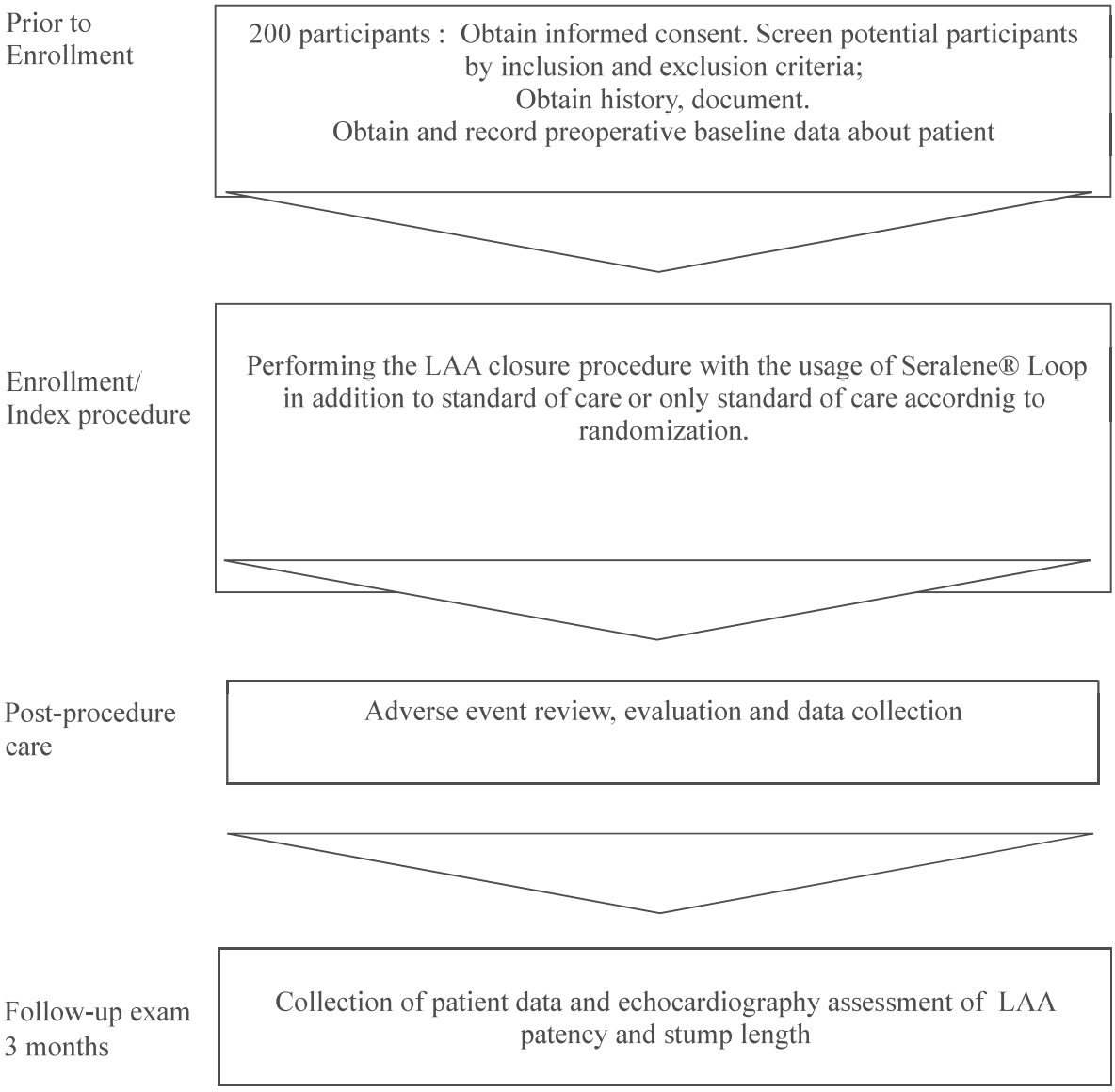
Intervention:

1. Experimental Group: Patients will undergo LAA closure during cardiac surgery using Seralene® Loop in addition to standard surgical care.

Objectives for LAA Closure During Cardiac Surgery Trial Involving LAA Patency after 3 Months:

1. **Primary Objective:**
    - To evaluate the patency rate of the left atrial appendage (LAA) following closure during cardiac surgery at the 3-month follow-up.
2. **Secondary objectives:**
    - To assess the safety and efficacy of LAA closure during cardiac surgery in terms of:
        - Incidence of stroke or systemic embolism within 3 months postsurgery.
        - Major bleeding events within 3 months post-surgery.
        - All-cause mortality within 3 months post-surgery

4.2. SCHEMA


Prior to Enrollment
200 participants : Obtain informed consent. Screen potential participants by inclusion and exclusion criteria;
Obtain history, document.
Obtain and record preoperative baseline data about patient
Enrollment/ Index procedure
Performing the LAA closure procedure with the usage of Seralene® Loop in addition to standard of care or only standard of care accordnig to randomization.
Post-procedure care
Adverse event review, evaluation and data collection
Follow-up exam 3 months
Collection of patient data and echocardiography assessment of LAA patency and stump length

5. STATYSTICAL ANALYSIS PLAN

Data will be analysed by descriptive and analytic stastistics. Descriptive statistics (measures of central thendency, measures of dispersion, and n (%)) will be calculated. Categorical data (sex, presence of comorbid condition, previous surgery, complications…) will be presented as n (%) and difference between study and control group will be tested with Hi squared test (or Fisher exact test) as appropriate.
Numerical data will be tested for normality of distribution (graphical and mathematical methods). According to normality of distribution data will be presented as means (for normally distributed data) or medians (min-max) for skewed data. Difference between two groups will be tested by T test or Mann-Whitney test as appropriate.

Univariate linear and logistic regression will be performed to identify independent variables (factors) which are significantly associated with dependent outcomes. Independent variables with $p<0.05$ will be included in multivariate linear and logistic regression. Univariate and multivariate linear and logistic regression will be performed for the group.

Hypothesis tests will be two-sided using the 0.05 significance level. Statistical analysis will be performed with IBM SPSS 21 (Chicago, IL, 2012) package.

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