Safety and Feasibility of Intra-Cardiac Echocardiography in Guiding Left Atrial Appendage Occlusion with the Watchman Device:

The ICE WATCHMAN study

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1.0 PURPOSE OF THE INVESTIGATION

The aim of this multi-center study will be to assess the feasibility and safety of left atrial appendage (LAA) occlusion with the WATCHMAN FLX™ device using a standardized intra-procedural intracardiac echocardiography (ICE) protocol under moderate sedation for procedural guidance. By eliminating the need for general anesthesia, we hope to show a reduction in procedural time, decrease use of supplemental invasive procedures (central venous line, invasive arterial pressure monitoring and transesophageal echocardiography) and quicker patient recovery time. This approach can decrease healthcare resource utilization and safely simplify left atrial appendage closure with the WATCHMAN device.

2.0 CLINICAL PROTOCOL

The study will be a prospective, non-randomized multicenter registry of 110 patients undergoing LAA closure with the WATCHMAN FLX utilizing an intra-procedural ICE probe under moderate sedation. The ***primary feasibility endpoint*** will be ability to successfully implant the WATCHMAN FLX device. Implant success is defined as confirmation of the device-specified release PASS (Position, Anchor, Size, Seal) criteria, successful device release, and adequate seal (defined as a residual leak <5 mm) as assessed by a core lab interpretation of the TEE (or CT) 45 days post-implant. The ***primary safety endpoint*** will be a composite of major complications (major bleeding [intracranial bleeding, or bleeding requiring blood transfusion], pericardial effusion requiring pericardiocentesis or surgery, device embolization, procedural-related stroke, or procedural related death). Additional measured end points will be: freedom from conversion to general anesthesia and/or standard TEE during implant, the incidence and the size of iatrogenic atrial septal defect on 45 day TEE (or CT). The ICE procedural images will also be collected and analyzed by an independent committee composed of non-implanting interventionalist, and an imaging specialist. The images will be graded in quality as optimal (TEE equivalent), acceptable (adequate but not as detailed as TEE), and inadequate. This prospective study, along with its endpoints will be registered in clinicaltrials.gov

2.1 SUBJECT SELECTION

A total of 3 sites will enroll up to 110 consecutive patients, allowing room for 10 withdrawals to ensure data is collected on 100.

2.2 INCLUSION CRITERIA

Determination for participation in the study is based on institutional standard of care practice for assessment of WATCHMAN FLX eligibility. Patients that are being considered for LAA Closure with WATCHMAN FLX device implant based on a history of non-valvular atrial fibrillation who are at increased risk for stroke and systemic embolism based on CHADS2VASc score >2 but have an appropriate rationale to seek a non-pharmacologic alternative to anti-thrombotic therapy due to risks of anti-thrombotic therapy. Patients should be able to tolerate the WATCHMAN FLX device implant procedure without the need for general anesthesia.

Key inclusion criteria:

- Men and Women $\geq$ 18 years of age
- The patients is eligible to undergo WATCHMAN FLX device implant procedure
- The patient is eligible for short term anticoagulation therapy
- Ability to tolerate the procedure without the need for general anesthesia as assessed by the treating physician(s)
- Ability to give informed consent for the procedure
- The patient is able and willing to undergo the procedure under moderate sedation
- The patient is able and willing to return for required 45-day TEE or computed tomography (CT) scanning.

2.3 EXCLUSION CRITERIA

No specific exclusion criteria will be implemented based on age, weight, body habitus, renal insufficiency, LAA anatomy, or the presence of sleep apnea or chronic lung disease. However, Patients will be excluded from the study if the treating physician(s) feel that general anesthesia is necessary to safely complete the procedure.

Key exclusion criteria:

- Patient has contraindication for short term anticoagulation
- The patient has history of a hypercoagulable state per medical record documentation
- Pregnancy or planning to get pregnant during the investigation

2.4 STUDY PROCEDURE

Pre-Procedure: Informed consent should be obtained from the patient prior to the start of the procedure or within 48 hours post-WATCHMAN FLX procedure if ICE protocol is utilized. Pre-procedural planning will be according to standard WATCHMAN FLX and local institution protocols. The use of cardiac CT is encouraged and should be performed shortly before the implant procedure (within 7-10 days) based on institutional protocols. Cardiac CT should be relied on as

the initial imaging modality to determine appendage anatomy, device sizing, and to exclude the presence of a LAA thrombus. In cases where CT scan cannot be performed prior to WATCHMAN FLX procedure, LAA thrombus will be excluded intraprocedural with ICE from the right atrium and/or pulmonary artery before transseptal puncture is completed. The treating cardiologist will screen the patient and deem them suitable for attempting the procedure with moderate sedation.

Procedure: ICE will initially guide all implants. The ICE probe type (size, model, etc.), venous access approach (two vs. three venous accesses), access to the LA (single transseptal two probes or two different transseptal) are left to the discretion of the treating physician. However, the ICE probe will be advanced into the LA in all cases to guide the implant. It may not be possible to obtain identical views to those of TEE (0^{O}, 45^{O}, 90^{O}, 135^{O}) with ICE. However, two orthogonal (short axis and long axis) views of the LAA should be obtained with ICE to document the position, compression, leak, and record the tug test and comply with the device release criteria (ICE-PASS). The two recommended positions to obtain short- and long- axis views are mid- left atrium and left ventricular inflow view (just underneath the mitral valve) as illustrated in Figure-1. The WATCHMAN FLX device implant will otherwise be performed in accordance with standard practice, with the Boston Scientific clinical specialist overseeing the procedure. This individual is required to document appendage anatomy characteristics, procedural times, and release criteria measurements and device compression. The WATCHMAN FLX device should not be deployed unless all release criteria are met. Indications for conversion to general anesthesia are at the discretion of the treating physicians and include, but are not limited to, hemodynamic instability, inability to maintain a protected airway during the procedure, inadequate cardiac imaging with ICE, and patient discomfort.

Post-Procedure: Patients should be monitored after the procedure according to institution specific protocol. Same day discharge for AM cases is allowed but not required. Patients should be maintained on a patient specific antithrombotic therapy for 45-day post-procedure based on the recommendation of the treating physician. Further anti-thrombotic changes should be made on a patient specific basis after consideration of the 45-day post-procedure TEE or CT scan and in accordance to WATCHMAN FLX device protocols.

The study specific de-identified data collection form will be used to collect procedural data and information regarding the study's primary and secondary endpoints for each case. A copy of this form, along with the pre-procedural CT imaging, procedural ICE images, and 45-day post procedure TEE or CT report should be compiled and sent to Mayo Clinic central repository database (Redcap) and Mayo Clinic Imaging Core Laboratory.

2.5 Study endpoints

The ***primary feasibility endpoint*** will be ability to successfully implant the WATCHMAN FLX device. Implant success is defined as confirmation of the device-specified release criteria on ICE (ICE-PASS), successful device release, and adequate seal (defined as a residual leak <5 mm) assessed by TEE or CT scan at 45 days' post-implant.

The ***primary safety endpoint*** will be a composite endpoint of major complications (major bleeding and/or life-threatening [intracranial bleeding, or bleeding requiring blood transfusion], pericardial effusion requiring pericardiocentesis or surgery, device embolization, procedural-related stroke, or procedural related death). An event is defined as procedure related if it occurred during or within 7 days of the procedure and deemed that the event was likely related to the device/procedure. If the information is insufficient, the conservative position (assuming procedure related) should be taken.

Secondary endpoints: These include freedom from conversion to general anesthesia and/or standard TEE during implant, incidence, and size of iatrogenic atrial septal defect at 45 days.

2.5.1 Sample size determination

The registry will enroll up to 110 patients, allowing room for 10 withdrawals to ensure data is collected on 100.

2.5.2 Outcome data and data analysis

Mayo Clinic Cardiovascular Imaging Core Laboratory will do data analysis.

2.5.3 Data and Safety Monitoring Committee

There will be no data and safety monitoring committee for this registry as the WATCHMAN FLX procedure is considered standard of care with either TEE or ICE at the participating institutions. Each site is expected to monitor appropriateness and outcomes of implant.

3.0 RISK ANALYSIS

Major procedural complications will be reported through the data collection form. However, since this is an observational registry that only collects clinical and imaging data from standard-of-care routine procedures, adverse events will not be separately reported to the IRB.

4.0 IRB INFORMATION

Each site is responsible for its own institutional review board.

5.0 ADDITIONAL RECORDS AND REPORTS

5.1 Data handling and record-keeping

Each institution will be responsible for individual data handling and record keeping. A Data collection sheet will be used to record procedure related characteristics and track any complications. The site-specific primary investigator will be responsible for this form's accuracy and completeness. Data forms, CT, and TEE images should be de-identified and sent to the Mayo Clinic Laboratory from all participating institutions for data analysis.

5.2 Record maintenance and retention

Originals of all images, WATCHMAN FLX Implant Form, and data collection form will be maintained at each site. A copy of this information should be sent to the study primary investigator.