Evaluation of the hemocompatibility of the **D**irect **O**ral **A**nti-**C**oagulant apixaban in **L**eft **V**entricular **A**ssist **D**evices (**DOAC LVAD**)

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1 List of Abbreviations

Abbreviation	Definition
ACC	American College of Cardiology
AHA	American Heart Association
AE	Adverse Event
AF	Atrial Fibrillation
CC	Coordinating Center
CNS	Central Nervous System
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
DOAC	Direct Oral Anticoagulant
EE	Expedited Event
ER	Emergency Room
GIB	Gastrointestinal Bleeding
HF	Heart Failure
INR	International Normalized Ratio
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
ITT	Intention to Treat
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate Dehydrogenase
LV	Left Ventricular
LVAD	Left Ventricular Assist Device
NVAF	Non-valvular Atrial Fibrillation
NYHA	New York Heart Association
RCT	Randomized Clinical Trial
SAE	Serious Adverse Event
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism

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3 EXECUTIVE SUMMARY

Title	Evaluation of the hemocompatibility of the **D**irect **O**ral **A**nti-**C**oagulant apixaban in **L**eft **V**entricular **A**ssist **D**evices (**DOAC LVAD**)
Indication	Heart failure with reduced ejection fraction patients supported with a continuous flow left ventricular assist device (LVAD).
Location	Inova Heart and Vascular Institute at Inova Fairfax Medical Campus
Brief Rationale	Adverse effects such as stroke and gastrointestinal bleeding (GIB) continue limit widescale adoption of LVAD therapy. Despite a reduction of stroke or neurologic dysfunction with the newer generation LVADs, stroke remains the leading cause of mortality accounting for 19% of deaths. Gastrointestinal bleeding is one of the most common adverse event for patients with LVADs, occurring most often in the first 3 months and affecting up to 25% of patients within the first year.[3] The HeartMate 3 (HM3) LVAD is a fully magnetically levitated centrifugal flow device which was designed to improve hemocompatibility by decreasing surface contact activation, widened gaps between the rotor and pump housing, and through the addition of artificial intermittent pulsatility by fluctuating the rotor speed every 2 seconds. In the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3), HM3 decreased the composite endpoint of survival at 2 years free of disabling stroke or reoperation to replace or remove a malfunctioning device compared to the HeartMate II axial flow device.[4] Patients with a HM3 LVAD require chronic antithrombotic therapy with a vitamin K antagonist (VKA) and antiplatelet therapy with aspirin 81-100 mg as outlined in the instructions for use (IFU).[5] Even in patients with excellent INR control, bleeding and thrombotic events are common and difficult to predict.[7] Direct oral anticoagulants (DOACs) have become first-line anticoagulant therapy for patients with atrial fibrillation (AF) and venous thromboembolism (VTE).[8,9] DOACs FDA approved for stroke prevention in AF or treatment of VTE include the direct thrombin inhibitor, dabigatran, and factor Xa inhibitors, apixaban,

	edoxaban, and rivaroxaban. When compared to warfarin for stroke prevention in AF, apixaban is the only DOAC to demonstrate superior efficacy and lower bleeding rates.[10–12] **Hypothesis:** In patients with a HM3 LVAD, treatment with apixaban for 24 weeks will be non-inferior with respect to freedom from death or hemocompatibility related adverse events (stroke, device thrombosis, bleeding, and arterial non-CNS thromboembolism), compared to treatment with warfarin.
Study Design	This pilot study will be a prospective, randomized, controlled, open label, trial of LVAD patients with 1:1 randomization to either apixaban or warfarin. Approximately 40 patients will be randomized into the study.
Treatment	Apixaban (Eliquis) or warfarin
Primary Objective and Endpoint	Freedom from death or hemocompatibility related adverse events (stroke, device thrombosis, bleeding, aortic root thrombus, and arterial non-CNS thromboembolism) at 24-weeks.
Secondary Objectives and Endpoints	1. Survival free of any stroke 2. Survival free of ischemic stroke 3. Survival free of hemorrhagic stroke 4. Survival free of device thrombosis 5. Survival free of gastrointestinal bleeding 6. Survival free of major non-gastrointestinal bleeding 7. All-cause mortality 8. Cardiovascular mortality

4 OBJECTIVES AND ENDPOINTS

4.1 Primary Objectives

The primary objective is to evaluate the safety of apixaban as compared to warfarin in LVAD patients.

Hypothesis: In patients with a HM3 LVAD, treatment with apixaban for 24 weeks will be non-inferior with respect to freedom from death or hemocompatibility related adverse events (stroke, device thrombosis, bleeding, aortic root thrombus, and arterial non-CNS thromboembolism), compared to treatment with warfarin.

4.2 Secondary Objectives

1. Survival free of any stroke
2. Survival free of ischemic stroke
3. Survival free of hemorrhagic stroke
4. Survival free of device thrombosis
5. Survival free of aortic root thrombus
6. Survival free of gastrointestinal bleeding
7. Survival free of major non-gastrointestinal bleeding
8. All-cause mortality
9. Cardiovascular mortality

4.3 Tertiary Objectives

1. Time in the therapeutic range for patients on warfarin
2. Anti-Xa trough concentration at 4 weeks, 12 weeks, and 24 weeks for patients on apixaban
3. A subgroup analysis of above endpoints will be completed for patients enrolled immediately after LVAD implantation versus those enrolled ≥ 3 months from LVAD implantation

5 BACKGROUND

Compared with optimal medical management, LVADs reduce heart failure symptoms, improve quality of life and decrease mortality in patients with New York Heart Association class IIIb/IV heart failure (HF) symptoms.[1,2] Unfortunately, adverse effects such as stroke and gastrointestinal bleeding (GIB) continue limit wide scale adoption of the therapy. Despite a reduction of stroke or neurologic dysfunction with the newer generation LVADs, stroke remains the leading cause of mortality accounting for 19% of deaths. Gastrointestinal bleeding is one of the most common adverse event for patients with LVADs, occurring most often in the first 3 months and affecting up to 25% of patients within the first year.[3]

The HeartMate 3 (HM3) LVAD is a fully magnetically levitated centrifugal flow device which was designed to improve hemocompatibility by decreasing surface contact activation, widened gaps between the rotor and pump housing, and through the addition of artificial intermittent pulsatility by fluctuating the rotor speed every 2 seconds. In the Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate 3 (MOMENTUM 3), HM3 decreased the composite endpoint of survival at 2 years free of disabling stroke or reoperation to replace or remove a malfunctioning device compared to the HeartMate II axial flow device.[4] While hemocompatibility has improved with this device, in order to prevent device thrombosis and stroke, patients with a HM3 LVAD require chronic antithrombotic therapy with a vitamin K antagonist (VKA) and antiplatelet therapy with aspirin 81-100 mg as outlined in the instructions for use (IFU).[5] Vitamin K antagonists require careful titration to INR goal, as elevations in INR are associated with hemorrhagic events and subtherapeutic INR values associated with thrombotic events including device thrombosis and ischemic strokes.[6] Even in patients with excellent INR control, bleeding and thrombotic events are common and difficult to predict.[7]

Direct oral anticoagulants (DOACs) have become first-line anticoagulant therapy for patients with atrial fibrillation (AF) and venous thromboembolism (VTE).[8,9] DOACs are FDA approved for stroke prevention in AF or treatment of VTE include the direct thrombin inhibitor, dabigatran, and factor Xa inhibitors, apixaban, edoxaban, and rivaroxaban. When compared to warfarin for stroke prevention in AF, apixaban is the only DOAC to demonstrate superior efficacy and lower bleeding rates.[10–12] Unlike apixaban, all other DOACs are associated with increased rates of GIB when compared with warfarin, a complication already plaguing LVAD patients.[3]

DOACs have been slow to be adopted in patients with LVADs for multiple reasons. A publication in 2013 raised alarm for the efficacy and safety of DOACs in patients with a mechanical prosthesis. The Randomized, Phase II Study to Evaluate the Safety and Pharmacokinetics of Oral Dabigatran Etexilate in Patients after Heart Valve Replacement (RE-ALIGN) trial compared high doses of dabigatran with warfarin for patients with a mechanical heart valve.[13] This trial was terminated early due to safety events in the dabigatran group. Compared with warfarin, patients on dabigatran experienced a higher rate of stroke, myocardial infarction, valve thrombosis, and major and non-major bleeding. Simultaneously, a pilot study examined the safety of dabigatran in patients with LVADs. This trial was also terminated early due to excess thromboembolic and bleeding complications in the dabigatran group.[14] Mechanical heart valves trigger a prothrombotic state via thrombin production through the intrinsic clotting cascade (i.e. contact activation pathway). Standard dosing of dabigatran is insufficient to suppress this thrombin burst and higher doses which may sufficiently inhibit thrombin are prohibitive due to bleeding risk.[15] It is believed that vitamin K antagonists are more effective at preventing thrombin production through their upstream inhibition of the intrinsic and common coagulation pathways. Apixaban, which acts at the start of the common pathway inhibiting factor Xa and preventing thrombin production, may result in outcomes more similar to the standard of care, vitamin k antagonists.

A second reason DOACs have been slow to be adopted in patients with mechanical devices is due to lack of reversal agents in the event of a life-threatening bleed or need for urgent surgery such as transplantation. Andexanet alfa, the first direct reversal agent for apixaban and rivaroxaban, was FDA approved in 2018. Prior to 2018, non-specific hemostatic agents such as 4-factor prothrombin complex concentrate (4F-PCC) were used commonly for patients on oral factor Xa requiring urgent reversal due to bleeding complications or need for urgent surgery. In a multicenter retrospective analysis of patients on apixaban or rivaroxaban presenting with an intracranial hemorrhage treated with 4F-PCC, hemostatic efficacy was reported in 82% of patients.[16] This rate of hemostasis was the same as that found in the Andexanet Alfa, A Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors (ANNEXA-4) study, where excellent or good hemostasis was reported in 82% of patients presenting primarily with intracranial or gastrointestinal bleeding.[17] Because of significant cost, lack of data in patients requiring surgery, and the short duration of activity of andexanet alfa, many hospitals have maintained 4F-PCC as the agent of choice for oral factor Xa inhibitor reversal until additional data are available.

6 PRELIMINARY STUDIES (STUDY RATIONALE)

While no randomized control trials have evaluated the safety and efficacy of factor Xa inhibitors in patients with LVADs. Apixaban is currently being studied in a randomized trial of patients with On-X mechanical heart valves (NCT# 04142658). For patients with LVADs, the potential safety and efficacy of using apixaban as an anti-coagulant is supported by a mock loop study performed with the HeartWare HVAD which utilized a control (no antithrombotic therapy), blood from patients on warfarin, in vitro addition of apixaban approximating a dose of 2.5 mg twice daily, and in vitro addition of apixaban approximating a dose of 5 mg twice daily. In this study, time to clot formation was lowest in the control group (71 minutes) and similar for circuits with warfarin and in vitro apixaban 2.5 mg twice daily (80 minutes). No clot formation was identified for the mock loop containing in vitro apixaban 5 mg twice daily after 90 minutes.[18] In recent years there have been 4 case reports and case series totaling 53 patients with LVADs which found satisfactory outcomes using apixaban in patients non-compliant or failing warfarin therapy.[19–21] The retrospective nature of these reports, as well as the different types of LVADs and patient characteristics makes it difficult to draw reliable conclusions on the efficacy and safety of apixaban in preventing thromboembolic and bleeding complications.

7 STUDY DESIGN

7.1 Screening / Baseline

Patients will have an initial screening evaluation, at which time patient eligibility will be determined. Those who willing participants, who meet all entry criteria and are interested in study participation will be consented and enrolled.

7.2 Randomization Phase

This will be a 2-arm prospective, randomized, controlled, open label trial with an active treatment arm (apixaban).

Patients will be randomized 1:1 to apixaban or warfarin. Patients will be randomized using procedures determined by the Coordinating Center (CC) to one of the two treatment groups.

7.3 Study Intervention Phase

Study treatment will be using the target dose of apixaban 5mg po BID or warfarin po daily for a goal INR of 2.0 to 2.5. All patients will be treated with aspirin 81mg daily as per the IFU. Randomized participants will receive the first dose of study drug as follows:

- **LVAD patients randomized to warfarin** will begin treatment once all anticipated surgical procedures are complete and the patient is deemed stable for transfer out of the ICU. Warfarin will be overlapped with low intensity heparin until the INR is at least 2.0. Warfarin will be dosed to maintain an INR goal of 2.0-2.5. For ambulatory LVAD patients, warfarin therapy will be continued.
- **LVAD patients randomized to apixaban** will transition from heparin to apixaban once all anticipated surgical procedures are complete and the patient is deemed stable for transfer out of the ICU. Heparin will be discontinued at the same time apixaban is initiated. For ambulatory LVAD patients on warfarin, warfarin will be transitioned to apixaban when the INR < 2.0.

Dose adjustments of apixaban will not occur. Dose adjustments of warfarin will be made no less than every 4 weeks to achieve the goal INR of 2.0 to 2.5. Participants will return to clinic according to the schedule shown in Appendix C.

For patients upgraded on the transplant list from a status 4 or below to a status 1-3, apixaban will be transitioned to warfarin, to allow for drug reversal at time of transplant. Patients randomized to the apixaban arm will be replaced to ensure 20 LVAD patients are exposed to apixaban over the duration of the study. Warfarin patients will not be replaced, as warfarin is standard of care therapy for LVAD patients.

7.4 Biobank Study

Biobank samples will be collected for future biomedical research to examine the impact of apixaban on markers of inflammation and the coagulation system. Candidate biomarkers may predict drug response to the treatment. Biomarker blood samples will be collected at the time points indicated in the schedule of events.

Samples will be collected at the study site into a lithium heparin, EDTA, serum and citrate tube. ~25 to 30cc of blood will be collected, processed, and stored for up to 7-years after study completion. No DNA analyses will be performed.

Investigators will not receive the results of analyses during the study, and no alerts will be sent.

8 PATIENT POPULATION

8.1 Study Population

It is anticipated that approximately 40 patients meeting eligibility criteria listed below will be randomized into the study. Participants suitable for this protocol are individuals already implanted with a HM3 LVAD. Patients may be currently hospitalized or ambulatory**. Enrollment of existing HM3 LVAD patients, implanted ≥ 3 months will be capped at 20 patients** to ensure adequate representation of newer LVAD implants who have a higher risk of thromboembolic adverse events.

8.2 Inclusion Criteria

1. Patients implanted with a HM3 LVAD
2. Age ≥ 18 years and able to provide written informed consent
3. Females of childbearing age must agree to use adequate contraception

8.3 Exclusion Criteria

1. History of post-LVAD device thrombosis, stroke, or gastrointestinal bleeding
2. Patients who are bridge to transplant and a current UNOS status 1-3
3. Ongoing inotrope therapy after LVAD (e.g., milrinone, dobutamine, epinephrine)
4. Permanent right ventricular assist device at the time of LVAD implant
5. Patients with a mechanical heart valve
6. Patients with end-stage renal disease on dialysis
7. Pregnant patients
8. Known history of ischemic stroke, intracranial bleed, or neurosurgery within 3 months
9. Known history of intracerebral arteriovenous malformation, cerebral aneurysm or mass lesions of the central nervous system.
10. Recent (<48 hours) or planned spinal or epidural anesthesia or puncture
11. Prior history of known thrombophilia (e.g., factor V Leiden, prothrombin gene mutation, protein C or S deficiency, antithrombin 3 deficiency, hyperhomocysteinemia, antiphospholipid antibody syndrome) or indication for higher INR goal (>2.5) with warfarin.
12. Thrombolysis within the previous 7 days
13. Patients with an allergy or contraindication to aspirin, warfarin, or apixaban
14. Patients on antiplatelet therapy other than aspirin (e.g., clopidogrel, prasugrel, ticagrelor, dipyridamole, or pentoxifylline)
15. Patients on combined P-glycoprotein and strong CPY3A4 inhibitors or inducers (e.g., fluconazole, posaconazole, rifampin)
16. Known bleeding within the last 30 days requiring emergency room presentation or hospitalization

17. Known history of an inherited bleeding disorder (e.g., hemophilia, von Willebrand disease)
18. Patients with active bleeding or a hemoglobin < 8.0 g/dl
19. Total bilirubin > 2.0 mg/dl, shock liver, hepatic encephalopathy, or biopsy proven liver cirrhosis
20. INR > 2.0 not due to anticoagulation therapy
21. Platelet count <100,000 cells/mm^3

9 TREATMENT

9.1 Intervention

This will be a 2-arm prospective, randomized, controlled, open label trial with an active treatment arm (apixaban). The therapeutic intervention will be treatment with either apixaban or warfarin.

Study drug will be given for 24 weeks for primary endpoint data.

Warfarin dose will be determined based on hospital protocol (Appendix A). The INR will be checked daily while inpatient. For outpatients INR will be checked at least weekly until two consecutive values are in range at which point INRs will be checked every 2-4 weeks.

9.2 Drug Dispensing

Apixaban will be manufactured by Bristol Myers Squibb Co. and provided by the Inova Health System Research Pharmacy. Apixaban will be supplied in bottles containing 5-mg (normal dose) tablets. Warfarin will be prescribed per normal prescribing practices and available through the patient's normal pharmacy. Participants will receive a sufficient supply of study drug at each study visit to last until the next study visit. Drug storage, inventory, accountability, and dispensing will be managed by and unblinded pharmacist at the CC. Patients will be instructed to take the medication as required by the protocol and compliance will be assessed at each visit (as described in the protocol).

9.3 Drug Administration

Participants will take apixaban twice daily by mouth or warfarin daily, according to the Dosing Guidelines below. The total number of anticoagulation pills taken will be 1-2 pills per day.

9.4 Drug Storage Requirements

Store at 25°C (77°F) with excursions between 15°C and 30°C (59°F and 86°F) permitted [see USP Controlled Room Temperature]. Protect from moisture.

9.5 Drug accountability

Participants are instructed to return all used, partly used, and unused trial product (apixaban) at each study visit. Returned trial product(s) (used, partly used or unused including empty packaging material) must be stored separately from the non-allocated trial product(s) until drug accountability has been reconciled. The investigators will keep track of all received, used, partly used and unused trial products.

9.6 Destruction

Used and unused study drug may be destroyed at the site according to accepted pharmacy practice, local and national guidelines, using the site's destruction procedure after the CRA has reviewed drug accountability and approved and accounted for the study drug to be destroyed. A copy of the site drug destruction SOP should be maintained in the Pharmacy section of the Regulatory Binder. Study drug destruction should be documented in the comments section of the Participant Specific Drug Accountability Log.

9.7 Randomization, Stratification and Blinding

Patients will be consented, enrolled, and randomized at the first study visit. Participants will be randomized using procedures determined by the CC to one of 2 treatment groups. Participants will be randomized in a 1:1 allocation ratio using a permuted block design with stratification based on time from LVAD implant (<3 months v. ≥ 3 months). Enrollment of existing HM3 LVAD patients, implanted ≥ 3 months will be capped at 20 to ensure adequate representation of newer LVAD implants who have a higher risk of thromboembolic adverse events.

9.8 Concomitant Medication

Participants should be treated per clinical center practice with standard HF medical therapy (diuretics for congestion, beta-blockers, mineralocorticoid receptor antagonists and sacubitril/valsartan or if intolerant or unable to afford this medication and angiotensin II receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACE-I).

10 RECRUITMENT AND SCREENING PROCEDURES

10.1 Common Recruitment Procedures

All LVAD patients followed at Inova Health System will be screened by a study coordinator. Patients meeting eligibility criteria will be approached regarding participation in this study.

10.2 Estimated Enrollment Period

This study will randomize approximately 40 at one-center in the U.S. The anticipated enrollment period is approximately 12-24 months.

10.3 Informed Consent Procedures

10.1.1 Informed Consent

Center clinicians will explain to eligible patients the purpose of the study, study interventions and evaluations, and the potential risks and benefits of participation, and will answer any questions. If a patient agrees to participate in the study, they will review and sign the site-specific IRB approved informed consent form (ICF).

10.1.2 Confidentiality and HIPAA Requirements

All information collected on study participants will be stored in a confidential manner. Only approved study personnel will have access to data collected as part of the study. Consented study participants will be identified by a participant ID number on all study documents. Data will be stored securely using standard operating procedures.

10.1.3 Protections of Human Subjects

Protections for human subjects of research are required under Department of Health and Human Services (HHS) regulations at 21 CFR parts 50, 56, and 312.

10.1.4 Summary of the Risks and Benefits

Blood draws: The risks of drawing blood include bleeding at the puncture site, bruising and pain. These occur in a very small portion of the population.

Eliquis (apixaban): Direct oral anticoagulants, the class to which apixaban belongs to, have been shown to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF). These agents are recommended over warfarin in eligible patients with NVAF and a CHA2DS2-VASc score ≥ 2 in men or ≥ 3 in women to reduce the risk of stroke and systemic embolism (1, LOE A). The risks for apixaban use in LVAD patients in this study are not known, particularly the risks associated with device thrombosis or stroke, but the risks are expected to be similar as use of apixaban for the prevention of stroke and systemic embolism in patients with NVAF. The most common (>1%) adverse reactions are related to bleeding as apixaban may cause serious, potentially fatal, bleeding. Compared with warfarin, DOACs reduce the risk of intracranial hemorrhage. Apixaban is not known to be teratogenic however it should not be used in pregnancy due to the increased risk of bleeding.

Coumadin (warfarin): Warfarin was the comparator to all DOACs in studies evaluating DOAC use for patients with NVAF. Warfarin is standard anticoagulation for LVAD patients. Warfarin is recommended in patients with atrial fibrillation and a CHA2DS2-VASc score ≥ 2 in men or ≥ 3 in women to reduce the risk of stroke and systemic

embolism who are not considered eligible for a DOAC (moderate-to-severe mitral stenosis or a mechanical heart valve) (1, LOE A). The most common (>1%) adverse reactions are related to bleeding as warfarin may cause serious, potentially fatal, bleeding. Warfarin is associated with a higher risk of intracranial and gastrointestinal bleeding when compared with apixaban in NVAF and VTE. Warfarin is known to be teratogenic and should be avoided in the first trimester of pregnancy.

11 VISIT SCHEDULE AND ASSESSMENTS

11.1 Baseline Evaluation and Randomization Visit

A complete schedule of assessments throughout the study is given in Appendix B.

Study Visit 0 (Enrollment & Randomization **after LVAD implant**)
This visit will include the screening and informed consent process followed by a baseline assessment including:

- Demographic information
- Medical history including review of history of thromboembolism and atrial fibrillation
- Physical examination including height and weight
- Review of medications
- Local laboratory testing, including white blood cells, hemoglobin, platelet count, sodium, potassium, BUN, creatinine, magnesium, AST/ALT, total and direct bilirubin, albumin, total protein, alkaline phosphatase, activated partial thromboplastin time, prothrombin time/INR, LDH, fibrinogen, and d-dimer. Labs obtained within 1 week prior to randomization can be used to assess patient eligibility and apixaban dosing.
- Serum or urine pregnancy test on all women of childbearing potential
- Biobank blood collection
- Verification of listing status for transplant

At this visit, participants will be randomized to either apixaban or warfarin. Doses will be assigned in the following fashion:

In ambulatory patients assigned to warfarin, they will remain on their current warfarin dose adjusted to achieve an INR of 2.0-2.5.

For inpatients assigned to warfarin, warfarin dose will be determined based on the hospital protocol (Appendix A). Warfarin dose will be titrated and overlapped with heparin until an INR of 2.0-2.5 is reached.

In ambulatory patients randomized to apixaban a baseline INR will be obtained. Warfarin will be held until INR < 2.0 and the apixaban will be initiated at a dose of 5 mg BID.

For inpatients randomized to apixaban, apixaban will be initiated as first-line oral anticoagulation at a dose of 5 mg BID. Heparin will be discontinued at the time of apixaban initiation. No overlap should occur.

11.2 Follow-up Evaluations

Study Visit 1 (2 weeks post-randomization +/- 7 days) – Virtual Visit

At this visit, two weeks after randomization, interim history, review of medications, adherence and tolerance assessment, and adverse event monitoring.

Study Visit 2 (4 weeks post-randomization +/- 7 days)

At this visit, four weeks after randomization, interim history, review of medications, physical examination, laboratory testing (white blood cells, hemoglobin, platelet count, sodium, potassium, BUN, creatinine, magnesium, AST/ALT, total and direct bilirubin, albumin, total protein, alkaline phosphatase, activated partial thromboplastin time, prothrombin time/INR, LDH, fibrinogen, d-dimer and Anti-Xa level), adherence and tolerance assessment, and adverse event monitoring. A biobank blood collection will be performed. Verification of listing status for transplant to ensure ongoing eligibility for study participation.

Study Visit 3 (6 weeks post-randomization +/- 7 days) – Virtual Visit

At this visit, six weeks after randomization, interim history, review of medications, adherence and tolerance assessment, and adverse event monitoring.

Study Visit 4 (8 weeks post-randomization +/- 7 days) – Virtual Visit with Labs

At this visit, eight weeks after randomization, interim history, review of medications, adherence and tolerance assessment, and adverse event monitoring. Remote lab testing will include white blood cells, hemoglobin, platelet count, sodium, potassium, BUN, creatinine, magnesium, AST/ALT, total and direct bilirubin, albumin, total protein, alkaline phosphatase, prothrombin time/INR, LDH.

Study Visit 5 (12 weeks post-randomization +/- 14 days)

At this visit, 12 weeks after randomization, interim history, review of medications, physical examination, laboratory testing (white blood cells, hemoglobin, platelet count, sodium, potassium, BUN, creatinine, magnesium, AST/ALT, total and direct bilirubin, albumin, total protein, alkaline phosphatase, activated partial thromboplastin time, prothrombin time/INR, LDH, fibrinogen, d-dimer and Anti-Xa level), adherence and tolerance assessment, and adverse event monitoring. A biobank blood collection will be performed. Verification of listing status for transplant to ensure ongoing eligibility for study participation.

Study Visit 6 (18 weeks post-randomization +/- 14 days) – Virtual Visit

At this visit, eighteen weeks after randomization, interim history, review of medications, adherence and tolerance assessment, and adverse event monitoring.

Study Visit 7 (24 weeks after randomization +/- 14 days)

At this visit, 24 weeks after randomization, interim history, review of medications, physical examination, laboratory testing (white blood cells, hemoglobin, platelet count, sodium, potassium, BUN, creatinine, magnesium, AST/ALT, total and direct bilirubin, albumin, total protein, alkaline phosphatase, activated partial thromboplastin time, prothrombin time/INR, LDH, fibrinogen, d-dimer and Anti-Xa level), adherence and tolerance assessment, and adverse event monitoring. A biobank blood collection will be performed. Verification of listing status for transplant to ensure ongoing eligibility for study participation. After this visit, the study phase is complete.

At this visit patients will be provided the opportunity to continue open label apixaban therapy if randomized to apixaban arm of the study. Patients randomized to warfarin will continue warfarin therapy.

End of Study Visit or Visit 8 (28 weeks after randomization +/- 7 days) – Virtual Visit

At this visit, 28 weeks after randomization and 4 weeks after study drug completion, interim history, review of medications, and adverse event monitoring.

11.3 Phone and Other Media Follow-up

General procedures: At Study Visit 1, participants and study staff will define optimal times and phone numbers for the protocol-specified phone contacts to encourage compliance with study procedures. In addition video visit structure for follow-up study visits will be reviewed.

During the follow-up visits, the participant will receive:

- Reminder of appropriate study drug dose for the stage of the protocol.
- Confirm plans for future study visits
- Confirm need to bring study drug to future study visits.

12 OUTCOME DETERMINATIONS

12.1 Primary Endpoint

Freedom from death or hemocompatibility related adverse events (stroke, device thrombosis, bleeding, aortic root thrombus and arterial non-CNS thromboembolism) at 24-weeks.

12.2 Secondary Endpoints

1. Survival free of any stroke
2. Survival free of ischemic stroke
3. Survival free of hemorrhagic stroke
4. Survival free of device thrombosis
5. Survival free of aortic root thrombus
6. Survival free of gastrointestinal bleeding
7. Survival free of major non-gastrointestinal bleeding
8. All-cause mortality
9. Cardiovascular mortality

12.3 Tertiary Endpoints

1. Time in the therapeutic range for patients on warfarin
2. Anti-Xa trough concentration at 1 month, 3 months, and 6 months for patients on apixaban
3. A subgroup analysis of above endpoints will be completed for patients enrolled immediately after LVAD implantation versus those enrolled ≥ 3 months from LVAD implantation

13 METHODS TO PROMOTE ADHERENCE

13.1 Protocol Training

Protocol training and adherence will be a major focus of the investigator training. Based on our experience in prior studies, identifying and correcting non-adherence is best accomplished in a stepped approach. The site will be responsible for managing participant compliance with study drug administration and visit compliance.

13.2 Data Quality Reports

The CC will provide data quality reports for review and will follow-up to reemphasize the importance of adherence as needed. Significant non-adherence issues will be discussed with the principal investigator.

14 SAFETY MONITORING AND REPORTING

14.1 Institutional Review Board

The study protocol, consent form, and other study documents will be subject to IRB approval. Any amendments to the protocol, other than minor administrative changes, must be approved by the IRB before they are implemented.

14.2 Definitions

14.1.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in a participant, whether or not it is considered directly related to the drug or biologic related. An AE can therefore be any undesirable sign, symptom or medical condition occurring after starting study drug, even if the event is not considered to be related to the pharmaceutical product. Study drug includes the drug under evaluation, and any reference drug given during any phase of the trial. Safety monitoring for adverse events will begin upon randomization.

14.1.2 Suspected Adverse Reaction

A suspected adverse reaction (SAR) is any adverse event for which there is a reasonable possibility that the drug caused the event. “Reasonable possibility” suggests there is a causal relationship between the drug and the adverse event. “Suspected adverse reaction” implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

14.1.3 Serious Adverse Events (SAE)

An adverse event or suspected adverse reaction is considered serious if the investigator or sponsor believes any of the following outcomes occurred:

- Death
- Life-threatening AE: Places the participant at immediate risk of death at the time of the event as it occurred. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition above.

This determination is based on the opinion of either the investigator or sponsor (e.g., if either believes it is serious, it must be considered serious).

14.1.4 Laboratory Test Abnormalities

For laboratory test abnormalities that meet the definition of an SAE, that required the participant to have the investigational product discontinued or interrupted or required the participant to receive specific corrective therapy, the clinical diagnosis rather than the laboratory term will be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

14.1.5 Assessment of Causal Relationship

A medically qualified investigator must assess the relationship of any AE to the use of study drug, based on available information, using the following guidelines:

- **Not related:** There is not a reasonable causal relationship to the investigational product and the adverse event.
- **Unlikely related:** No temporal association or the cause of the event has been identified, or the drug or biologic cannot be implicated.
- **Possibly related:** There is reasonable evidence to suggest a causal relationship between the drug and adverse event.
- **Related:** There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

14.1.6 Assessment of Adverse Event Severity

The determination of adverse event severity rests on medical judgment of a medically qualified Investigator. The severity of AEs will be graded using the following definitions:

- **Mild:** Awareness of sign, symptom, or event, but easily tolerated.
- **Moderate:** Discomfort enough to cause interference with usual activity and may warrant intervention.
- **Severe:** Incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention.

Anticipated Disease Related Events and Events of Interest

The following are anticipated, disease-related events in patients with LVAD or anticipated events of interest in patients with apixaban or warfarin:

- Arrhythmias
- Cardiac Transplantation
- Device Explant
- Infection
- Transient Ischemic Attack
- Unplanned hospitalization, ER visit or clinic visit

Anticipated events will not be captured as AEs/SAEs during the study but will be entered on the appropriate electronic case report form (eCRF) module (“Anticipated Disease Related Events” page).

14.1.7 Recording and Reporting of Adverse Events

The site Investigator is responsible for monitoring the safety of participants enrolled into the study at the study sites. For this study, non-serious AEs will not be collected on the safety reporting page of the eCRF but should be documented in the source documents and followed according to local standard of care. Events significant enough to necessitate modification of antithrombotic therapy dosing will be captured on the appropriate eCRF module (“Adverse Events” page).

14.1.8 Subject Stopping Criteria and Drug Modification

For patients in the apixaban arm with a thromboembolic event (stroke, device thrombosis or arterial non-CNS thromboembolism), will be considered a study drug failure and converted to warfarin (withdrawn from active treatment). For patients experiencing a bleeding event, the aspirin will be discontinued. Only in patients with recurrent bleeding will the apixaban be discontinued (withdrawn from active treatment) and warfarin initiated at an INR goal of 1.5 to 2.0. Patients will continue to be followed per the study schedule through study completion.

For apixaban patients listed for transplant, who are upgraded to a status 1-3, the apixaban will be discontinued and the patient converted to warfarin. These patients will be followed until transplant or study completion. Each apixaban patient who does not complete the 6-month study duration will be replaced to ensure 20 patients are in the apixaban arm with complete follow-up.

For patients in the warfarin arm with a thromboembolic event, will be managed with a higher INR goal of 2.5 to 3.0. For patients experiencing a bleeding event, the aspirin will be discontinued. Only in patients with recurrent bleeding will the INR goal range be reduced to 1.5 to 2.0. For patients with a 3rd bleeding event, warfarin will be stopped, and the patient will be withdrawn from treatment and the patient followed according to the study protocol.

Any AE events occurring up to 72 hours after the study drug is discontinued will be considered a treatment-emergent adverse event.

All SAEs, except for those anticipated events listed above, occurring from signed informed consent through study completion will be captured on the AE eCRF. Unless exempted as described above**,** all SAEs, whether or not deemed drug-related or expected, must be reported to the IRB by the investigator or qualified designee within 24 hours of first becoming aware of the event. For this study, all-cause deaths will be reported on the AE eCRF. The investigator or qualified designee will enter the required information regarding the SAE into the appropriate module of the eCRF. If the eCRF system is temporarily unavailable, the event, including the investigator-determined causality to study drug should be reported via the back-up paper AE form. Upon return of the availability of the electronic data capture (EDC) system, the SAE information must be entered into the eCRF.

Follow-up
When additional relevant information becomes available, the Investigator will record follow-up information according to the same process used for reporting the initial event as described above. The Investigator will follow all reportable events until resolution, stabilization or the event is otherwise explained.

The investigator will follow all SAEs until resolution, stabilization, until otherwise explained or until the participant completes the final follow-up, whichever occurs first. Investigators are also responsible for promptly reporting AEs to their reviewing IRB/EC in accordance with local requirements.

14.1.9 Suspected Unexpected Serious Adverse Reaction

AEs that meet the criteria of serious, related to study drug, and unexpected per investigator brochure, qualify for expedited reporting to the regulatory authorities. The site Investigator will assess all SAE's occurring at his/her site and evaluate for "unexpectedness" and relationship to study drug. The site Investigator is required to complete and submit a voluntary MedWatch Report for events deemed, as serious, study drug related and unexpected at: https://www.accessdata.fda.gov/scripts/medwatch/.

A copy of this report should be kept at the site.

14.1.10 Pregnancy

Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported within the same timelines as a serious adverse event. The pregnancy will be recorded on the appropriate paper pregnancy tracking form. The pregnancy will be followed until final outcome. Any associated AEs or SAEs that occur to the mother or fetus will be recorded in the AE eCRF, within the EDC system.

15 STATISTICAL METHODS AND DATA ANALYSIS

15.1 General Design Issues

All planned analyses will be prospectively defined for this study and approved by the CC. The statistical analysis plan (SAP) will contain detailed information regarding the data analysis. The SAP will be finalized prior to trial completion and will be approved by the coordinating center statistical team.

Analysis of the DOAC LVAD Study will be based on intention to treat (ITT). That is, participants will be analyzed (and endpoints attributed) according to the treatment strategy to which participants are randomized, regardless of subsequent additional post-randomization treatment and medical care. The ITT population will correspond to all randomized participants. The primary and secondary analyses will follow the ITT principle.

Baseline demographic and clinical variables will be summarized for each randomized arm of the study. Descriptive summaries of the distribution of continuous variables will be presented in terms of percentiles (e.g., median, 25th and 75th percentiles) along with means and standard deviations. Categorical variables will be summarized in terms of frequencies and percentages.

In addition, exploratory analyses will be performed to help explain and understand findings observed from the planned analyses. Statistical tests with a p-value <0.05 will be considered statistically significant, unless otherwise stated. Analyses will be performed using SAS software (SAS Institute, Inc, Cary, NC).

15.2 Sample Size Justification and Randomization

Participants will be randomized in a 1:1 allocation ratio using a permuted block design with stratification based on the time from LVAD implant (<3 months or ≥3 months). The number of patients ≥3 months from LVAD implant will be capped at 20 participants. As this is an initial pilot study to assess safety and feasibility, we plan to enroll 40 patients.

For the primary purposes of this pilot study, each patient's data will be reviewed individually. Patients newly implanted vs previously implanted with a HM3 LVAD may be analyzed as distinct subgroups. The sample size of up to forty (40) implanted patients is based upon industry standards for early-stage studies of medical devices; the sample size was not statistically derived. This study is not designed to provide statistical significance of the outcomes. The study will provide data to be used for subsequent design and development of the phase III clinical trials. An interim report may be generated prior to completion of enrollment for regulatory or publication purposes.

15.3 Analysis of the Primary Endpoint

For the primary endpoint, a time-to-event analysis will be conducted. The Cox regression model for survival data will be used to test the statistical significance of differences in the composite endpoint (survival free of major hemocompatibility related adverse event) between the two treatment groups. Certain clinical covariates may be used in the regression model (age, sex, race, atrial fibrillation, history of stroke or bleeding prior to LVAD, early (<3 months) or late (≥3 months) after implant, laboratory parameters, hemodynamics, coagulation marker measures).

15.4 Analysis of Secondary and Tertiary Endpoints

The key secondary endpoint will be analyzed for time-to-event endpoints, using the Cox regression model for survival data will be used to test the statistical significance of differences in mortality between the treatments. Kaplan-Meier curves will be generated to graphically display the mortality rates as a function of time from randomization in each treatment. Patients will be censored when upgraded to a status 1-3, at the time of transplant, transfer of care to another LVAD center, device decommissioning or explant for myocardial recovery.

16 DATA MANAGEMENT PROCEDURES

16.1 Overview of Data Management

The CC will have primary responsibility for data management, including the development of data collection systems, data monitoring processes, and data storage and back-up. State-of-the-art technology will be used for the management of the network's data.

16.2 Data Security

Access to databases will be controlled centrally by the CC through user passwords linked to appropriate privileges. This protects the data from unauthorized changes and inadvertent loss or damage. Database and web servers will be secured by a firewall and through controlled physical access. Database back-up will be performed daily using standard procedures in place at the CC. All disk drives that provide network services, and all user computers, will be protected using virus-scanning software.

16.3 Publication Policy

Dissemination of preliminary information can adversely affect the objectivity of study data. For this reason, investigators will not be allowed to perform subset analyses at any point before the conclusion of the study, and any data, other than safety data, cannot be used for publication or reporting outside of this study until the study is completed or discontinued by the principal investigator.

17 STUDY ADMINISTRATION

17.1 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) has been convened to assess the progress of the clinical study, the safety data, and critical efficacy endpoints (if appropriate) and provide recommendations to the sponsor. The members of the DSMB serve in an individual capacity and provide their expertise, including recommendations regarding the continuation, modification, or termination of any or all arms of the study. The DSMB will review cumulative study data to evaluate safety, study conduct, scientific validity, and data integrity of the study. A separate DSMB charter outlines their roles and responsibilities.

17.2 Study Termination

The study may be terminated by the Sponsor at any time with suitable written notice to the reviewing IRB and applicable regulatory agencies. The study may be terminated by the DSMB based on concerns for significant harm to study participants based on criteria outlined in the DSMB charter. The following clinical events in the apixaban arm will result in an immediate pause of study enrollment for an evaluation by the independent DSMB:

- ≥ 2 thromboembolic events (ischemic stroke, arterial non-CNS embolism, device thrombosis, aortic root thrombus)
- ≥ 4 major bleeding events (Types 3-5)
- ≥ 2 deaths due to either thromboembolic events or major bleeding events

Patients who are already enrolled in the study will continue study-related activities during the enrollment pause.

18 REGULATORY ISSUES

18.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol. These procedures are designed to ensure adherence to Good Clinical Practice, as described in the following documents:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. US 21 Code of Federal Regulations Part 312, Food and Drug Administration Investigational New Drug Application

The investigator agrees to adhere to the instructions and procedures described in the protocol and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

18.2 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form, and other information to participants must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC). Documentation that the protocol and informed consent have been approved by the IRB/IEC must be provided before study initiation. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

18.3 Informed Consent

The investigator or designee must explain to each participant (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each participant must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The informed consent form(s) must be submitted by the investigator for IRB/IEC approval.

18.4 Subject Withdrawal

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Should the subject be withdrawn from the study, the reason for withdrawal must be documented in the CRF.

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits.

18.5 Investigational New Drug (IND) Application

The investigator or designee will file for an investigational new drug (IND) with the Food and Drug Administration (FDA) prior to initiation of the clinical trial. This will permit the FDA to determine that apixaban is reasonably safe for initial use in LVAD patients. This is an investigator IND for an approved product (apixaban), that will be used in a new patient population (LVAD patients). This IND will not be used to change the labeling of apixaban.

19 APPENDICES

19.1 Appendix A – Warfarin Dosing Protocol

Inova Fairfax Medical Center Inpatient Warfarin **New Start** Guideline (Days 1 – 2)

If warfarin was intentionally held on admission for reason other than supratherapeutic INR (e.g., need for surgery), resume home dose on days 1-2 and then and then utilize Guideline for Days 3-7 thereafter

<table>
<tr><th colspan="4">Step 1: Assess for patient characteristics that may impact warfarin sensitivity</th></tr>
<tr><td colspan="2">Factors that increase warfarin sensitivity:
Baseline INR > 1.5
> 70 years of age
Decompensated HF
Significant liver disease
Weight < 60 Kg
Malabsorption syndrome
Chronic diarrhea
Malnourished
Hypoalbuminemia (esp < 2 g/dl)</td><td colspan="2">Factors that decrease warfarin sensitivity:
< 60 years of age
BMI > 30</td></tr>
<tr><th colspan="4">Step 2: Evaluate for severe and major drug-drug interactions</th></tr>
<tr><td colspan="2">Severe drug-drug interactions:
SMX/TMP
Metronidazole</td><td colspan="2">Major drug-drug interactions:
Azole antifungals
Macrolide antibiotics
Fluoroquinolones
Propafenone
Amiodarone or dronedarone
Disulfiram
Tamoxifen</td></tr>
<tr><th colspan="4">Step 3: Determine warfarin initiation dose</th></tr>
<tr><th>Warfarin 2.5 mg</th><th>Warfarin 4 mg</th><th>Warfarin 5 mg</th><th>Warfarin 7.5 mg</th></tr>
<tr><td>Any factor that increases warfarin sensitivity

OR

Any severe drug-drug interaction

OR

≥ 2 Major drug-drug interactions</td><td>No factor that increases warfarin sensitivity

AND

No severe drug-drug interactions

AND

1 major drug-drug interaction</td><td>No factor that increases warfarin sensitivity

AND

No severe or major drug-drug interactions</td><td>No factor that increases warfarin sensitivity

AND

No severe or major drug-drug interactions

AND

BOTH factors that decrease warfarin sensitivity</td></tr>
<tr><td colspan="4">Recommended starting dose is intended for days <u>1 and 2</u> of warfarin therapy.
Subsequently see “IFMC Inpatient Warfarin <u>New Start</u> Guideline (D3-D7)”</td></tr>
</table>

Inova Fairfax Medical Center Warfarin New Start Guideline (Days 3 – 7)

Day	INR Goal 2.0 – 2.5	**Instruction** In additional to instructions below, consideration should be given to the rate of INR increase/decrease, perceived warfarin responsiveness/sensitivity, initiation/discontinuation of interacting medications, and clinical status of the patient. The INR should increase 0.1 – 0.3 per day until steady state is achieved at approximately one week. **If INR increases ≥ 0.4 per day, decrease dose by 25 – 50%** **If INR increases ≥ 1 per day, HOLD a dose**
1 – 2	--	See "IFMC Inpatient Warfarin New Start Guideline (Days 1 – 2)"
3	< 1.5	1 – 2x initial dose
	1.5 – 1.9	Continue initial dose
	2.0 – 2.5	0.25 – 0.5x initial dose
	≥ 2.6	HOLD
4	< 1.5	1.5 – 2x initial dose
	1.5 – 1.9	1 – 1.5x initial dose
	2.0 – 2.5	Continue last dose
	2.6 – 2.9	0.75x last dose
	≥ 3.0	0.25x last dose or HOLD
5	< 1.5	2x initial dose
	1.5 – 1.9	1 – 2x initial dose
	2.0 – 2.5	Continue last dose
	2.6 – 2.9	0.5x last dose
	≥ 3.0	0.25x last dose or HOLD
6	< 1.5	2 – 3x initial dose
	1.5 – 1.9	1.5 – 2x initial dose
	2.0 – 2.5	Continue last dose
	2.6 – 2.9	0.75x last dose
	≥ 3.0	0.25x last dose or HOLD
7	< 2.0	2 – 3x initial dose
	2.0 – 2.5	Continue last dose
	2.6 – 2.9	0.8 – 0.9x last dose
	≥ 3.0	0.75x last dose or HOLD
See "IFMC Inpatient Warfarin Maintenance Protocol" for dosing after 7 days		

19.2 Appendix B – Adverse Event Definitions

- **Arrhythmias:** Any documented arrhythmia that results in clinical compromise, or requires hospitalization or treatment. Arrhythmias will be further classified as sustained ventricular arrhythmia or sustained supraventricular arrhythmia
- **Arterial non-CNS thromboembolism:** Acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by 1 or more of the following: 1) standard clinical and laboratory testing, 2) operative findings, 3) autopsy findings
- **Bleeding:** the location/source of the bleed will be recorded and subsequently categorized as follows; CNS bleeding will be captured under cerebrovascular event/stroke
    - Type 2: Any overt, actionable sign of hemorrhage that does not fit the criteria for Type 3, 4, or 5 but does meet at least one of the following criteria:
        - 1) requiring non-surgical, medical intervention by a healthcare professional
        - 2) leading to hospitalization or increased level of care; or
        - 3) prompting evaluation
    - Type 3a
        - Overt bleeding accompanied by hemoglobin drop of 3 to < 5 g/dL
        - Any transfusion with overt bleeding
    - Type 3b
        - Overt bleeding plus hemoglobin drop 5 g/dL or greater
        - Cardiac tamponade
        - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
        - Bleeding requiring intravenous vasoactive agents
    - Type 4: VAD implantation-related bleeding (includes concomitant cardiac or non-cardiac surgical procedure)
        - Reoperation after the closure of incision or incisions used to implant the VAD to control bleeding
        - ≥ 50 kg: ≥ 4U pRBC within any 48 hours during the first 7 days post-implant
        - < 50 kg: ≥ 20 cm^3/kg pRBC within any 24 hours during the first 7 days post-implant
        - Chest tube output > 2 liters within 24 hours
    - Type 5a: Probably fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
    - Type 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation
    - For all types of bleeding, the event will be classified as:
        - Patient-related (e.g., coagulopathy unrelated to surgical technique such as non-adherence with anticoagulation medication resulting in inappropriately high level of anticoagulation, hepatic failure)
        - Management-related (e.g., related to surgical technique, hypertension, bleeding in the setting of inappropriate levels of anticoagulation)
        - Pump-related (e.g., bleeding from the outflow graft, apical connector, or other internal components
- **Major bleeding**: Bleeding Types 3-5
- **Cerebrovascular event:** This refers to cerebrovascular accidents (stroke) of any cause (ischemic or hemorrhagic).
- **Device Explant:** This refers to LVAD explantation or LVAD decommissioning for myocardial recovery.
- **Device Thrombosis:** This refers to suspected or confirmed device thrombosis.
    - Suspected device thrombosis is a major device-related malfunction which clinical or device parameters suggest thrombus on the blood-contacting components of the pump, cannula, or grafts. Suspected device thrombosis will be defined as signs and symptoms to include at least 1 of the 3 following criteria:

        - 1) Presence of major hemolysis by LDH or clinical evidence of hemolysis by hemoglobinuria
        - 2) Presence of heart failure not explained by structural heart disease
        - Abnormal pump parameters consistent with diminished pump output/pump efficiency/pump performance

        And

    - Suspected device thrombus will be accompanied by 1 or more of the following events or interventions:
        - 1) Death
        - 2) Stroke or TIA
        - 3) Arterial non-CNS embolism
        - 4) De-novo need for inotrope therapy
        - 5) Treatment with IV anticoagulation, IV thrombolytics, or IV antiplatelet therapy
        - 6) Pump replacement
        - 7) Pump explanation with or without exchange
        - 8) Pump deactivation without pump removal
        - 9) Operation to repair or replace any internal components of the circulatory support system
        - 10) Urgent transplant listing (immediate urgent listing for transplant)
    - Confirmed device thrombosis is major device-related malfunction in which thrombus is confirmed within the blood-contacting surfaces of device inflow cannula or outflow conduit or grafts. This can be reported through direct visualization inspection or by incontrovertible contrast radiographic evidence or by the absence of an appropriate Doppler flow signal that results in or could potentially induce circulatory failure or result in thromboembolism
- **Gastrointestinal Bleeding:** This refers to bleeding from the gastrointestinal tract that is or is not identified.
- **Infection:** This refers to any infection requiring antibiotic or antifungal therapy.
- **Transient Ischemic Attack:** a transient neurologic deficit that may persist for up to 24 hours.
- **Unplanned hospitalization, ER visit or clinic visit:** This refers to any medical evaluation for an LVAD patient that is unplanned.
- **Aortic root thrombus:** thrombus located on the aortic valve or in the aortic cusp or aortic root which is visualized on echocardiography or CT imaging.

19.3 Appendix C – Schedule of Assessment

Visit number	0	1	2	3	4	5	6	7	Final Visit
Time of Visit	Enrollment & Randomization	2 weeks (±7D)	4 weeks (±7D)	6 weeks (±7D)	8 weeks (±7D)	12 weeks (±14D)	18 weeks (±14D)	24 weeks (±14D)	28 weeks (±7D)
Virtual Visit		x		x	x		x		x
Inclusion/Exclusion criteria	x								
Information & Informed consent	x								
Medical History & Concomitant Meds	x	x	x	x	x	x	x	x	x
Physical examination & Vitals	x		x			x		x	
Laboratory tests*– CBC, CMP, Mg, aPTT, PT/INR**, LDH, Fibrinogen and D-dimer	x		x		x†	x		x	
Anti-Xa Level (apixaban arm only)			x			x		x	
Biobank sample collection	x		x			x		x	
Pregnancy Test***	x								
Dispense study medication****	x		x			x			
Adverse events		x	x	x	x	x	x	x	x

*Labs obtained within 1 week prior to randomization can be used to assess patient eligibility and apixaban dosing.

**Additional INR monitoring may be required in the warfarin patients to achieve the protocol INR goal.

***Pregnancy test only required in females of childbearing potential (age < 50 years).

****Randomization will occur at enrollment. Study drug treatment will be initiated as described in protocol above.

†Week 8 visit is conducted virtually, remote labs to be collected include: CBC (white blood cells, hemoglobin, platelet count), CMP (sodium, potassium, BUN, creatinine, magnesium, AST/ALT, total and direct bilirubin, albumin, total protein, alkaline phosphatase), prothrombin time/INR, LDH.

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