Ventricular Assist Device Anti-Factor Xa (VAD-AntiX) monitoring study: a prospective randomized feasibility trial

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SYNOPSIS

Study Title	Ventricular Assist Device Anti-Factor Xa (VAD-AntiX) monitoring study: a prospective randomized feasibility trial
Objective	I. Demonstrate the feasibility and success of implementing nomograms for heparin administration based on both aPTT measurement and anti-factor Xa activity. • Feasibility will be determined by: 1) Questionnaires evaluating the practicality and acceptably of the nomograms 2) The percentage of correct dosing adjustments made by the nursing team required to achieve first therapeutic anticoagulation according to the specified directions provided. • Success will be determined by 1) number of dosing changes required to achieve first therapeutic anticoagulation 2) time (in hours) until achievement of first therapeutic anticoagulation 3) percentage of time therapeutic anticoagulation remains after it is achieved II. a. Explore heparin dosing and the concordance between the aPTT and anti-factor Xa activity in this patient population. b. Explore clinical outcomes related to the heparin monitoring nomograms, including major bleeding, neurologic events, gastrointestinal bleeding and pump thrombosis.
Study Period	Planned enrollment duration: 1 year Planned study duration: 1 year
Number of Patients	20 evaluable
Study Treatment	Monitoring and adjusting heparin anticoagulation utilizing aPTT based heparin nomograms OR anti-factor Xa based heparin nomograms
Study Design	Prospective Randomized
Inclusion and Exclusion Criteria	Inclusion: 18 years and older undergoing LVAD implantation Exclusion: Patient unable to receive heparin or known hypercoagulable disorder, prisoners, pregnancy, or lactating women.
Measurements	Detailed records will be collected using a REDCap database. Baseline labs will be obtained as well as aPTT and anti-factor Xa while on the heparin dosing nomogram/intervention. Heparin and coumadin dosing details will be obtained. Clinical outcomes will be monitored.
Statistical Methodology	Chi Square and descriptive statistics used for questionnaire responses. Mann Whitney U test for dosing adjustments and time until first anticoagulation. Students t test or Mann Whitney U for dosing changes required, time until therapeutic anticoagulation, and percentage of time therapeutic anticoagulated

	Concordance assessed with mixed effects model; repeated measures ANOVA and Turkey's test for multiple comparisons to analyze heparin administration. Clinical outcomes will be compared with a Chi square test. Intention to treat analysis will be used.

A Background and Rationale

Mechanical Circulatory Support

The prevalence of heart failure in the United States currently exceeds five million and continues to rise.[1] It remains the primary diagnosis in over one million hospitalizations annually, with an economic burden exceeding $30 billion in the United States.[2] People with severe heart failure and symptoms at rest may be treated with mechanical circulatory support (MCS) pumps, such as a left ventricular assist device (LVAD). This pump is used as a long-term destination therapy or as a bridge to receiving a heart transplant. As the number of organ donors remains relatively fixed, and conventional medical therapies fail, MCS is increasingly utilized in this patient population with total implants approaching 2,500 per year. [3]

Complications of Mechanical Circulatory Support

As the incidence of MCS implantation increases, it is important to recognize the risks associated with these devices. The balance between bleeding and thrombotic complications is complex and often pose a therapeutic challenge to clinicians, as both are common and devastating, especially in the early postoperative period. Thrombus formation leads to potentially life-threatening outcomes such as stroke, heart attack and device failure. Pump exchange as a treatment for device failure has been associated with a reduction in subsequent 1-year survival. [3] Furthermore, in the recent era of MCS utilization, there has been higher event rates of hemolysis, stroke, and pump exchange than in previous eras. [3,4] Although thrombosis risks are on the rise, bleeding still remains the most common complication after LVAD implantation.[5] Excessive anticoagulation can lead to serious and often fatal hemorrhage, including exsanguination from surgical sites, intracranial hemorrhage, retroperitoneal and gastrointestinal bleeding. Despite advancements in the management and understanding of these devices over the years, bleeding requiring re-exploration remains greater than 20%, and the requirement for transfusion of two or more packed red blood cells exceeds 50% over the first 30 days [6].

Pharmacologic Management to Prevent Thrombosis

One management strategy utilized to minimize the risk of thrombus formation within these devices is the early administration of therapeutic anticoagulation with intravenous (IV) unfractionated heparin (UFH) postoperatively. Current anticoagulation management recommendations include postoperative bridging with IV UFH, targeting

activated partial thromboplastin time (aPTT) goals ranging from 40 to 80 seconds, followed by warfarin dosed to an international normalized ratio (INR) goal of 2.0 to 3.0. Additionally, an antiplatelet agent, such as aspirin and/or clopidogrel or dipyridamole, is recommended. [5 7 8] Warfarin causes a transient prothrombotic period after initiation because of its variable effect on both procoagulant and anticoagulant factor activity over time. These opposing effects are due to the timing of inhibition of specific factors before the balanced decrease of vitamin K-dependent clotting factor levels is achieved. Therefore, a bridging period with IV UFH is recommended. [9] Although expert guidelines and device specific recommendations have been made regarding pharmacologic management, wide variation exists between medical centers with regards to timing and dose of IV bridging strategies and patient-specific monitoring parameters and goal[10].

Monitoring UFH Therapy: aPTT vs. anti-Xa

The pharmacokinetics of UFH are unpredictable due to the binding of UFH to a number of plasma proteins, macrophages, and endothelial cells. Additionally, the response varies among patients so it is routine practice to monitor heparin frequently and adjust the dose based on the results of a coagulation test.[9] The aPTT, a plasma based assay measuring activity of intrinsic and common coagulation pathways, has been the most widely used method to monitor IV UFH. Interestingly, the data that support adjusting heparin doses to maintain a therapeutic aPTT range are based on weak evidence[11], and heparin dosing and monitoring has not been rigorously studied in patients with LVADs. The International Society for Heart and Lung Transplantation MCS guidelines recommend titrating heparin to a target aPTT of 60-80 seconds, despite these known limitations.[5] Although the aPTT is widely available, relatively inexpensive and has gained long term familiarity, many problems with the use of this assay have been identified. The assay is susceptible to physiological and nonphysiological factors that do not reflect intrinsic heparin activity, causing patients to receive unintentionally high or low doses of heparin.[12] Lupus anticoagulant and factor XII deficiency may overestimate the aPTT. Common clinical features of patients with LVADs such as liver disease, consumptive coagulopathy, concurrent warfarin administration and hemolysis may also overestimate the aPTT. On the other hand, low antithrombin levels and elevated factor VIII levels may attenuate the expected aPTT response.[12] Unlike the aPTT assay, the anti-Xa activity assay is a more direct measure of UFH and is unaffected by the presence of lupus anticoagulant, liver disease, or consumptive coagulopathy. Furthermore, in comparison with the aPTT, the correlation between anti-Xa activity and heparin concentration is more robust, the target therapeutic range is better defined, and anti-Xa activity is resistant to variability in the setting of stress and inflammation, which are features of the acute postoperative period. Conversely, this assay is not as widely available as the aPTT, may incur higher costs and may underestimate heparin concentrations in the setting of hemolysis or low antithrombin levels. In addition, elevated triglyceride or bilirubin levels may falsely lower the results.[13] The known strengths and limitations of both assays make it challenging to determine which method of heparin monitoring is ultimately superior.[12]

Previous Research and Preliminary Data

Evidence of superiority of monitoring IV UFH effects with the anti-Xa assay in terms of safety and effectiveness is lacking. Studies have consistently noted the discordance between the aPTT and the anti-Xa assay in various adult and pediatric populations.[14,15,16,17,18,19,20,21,22,23,24,25,26] In adult patients with LVADs specifically, concordance rates between the assays have been reported as low. [14,15] Based on four patients with LVADs at our institution (Figure 1.), the average relationship between the aPTT and the anti-Xa assay is shown (solid blue line). The dashed green line represents ideal concordance between the assays. Most of the data points show considerable scatter from both the average (solid black) and ideal (dashed green) relationships. The crude correlation co-efficient (not accounting for repeated measures) is 0.44. When values from both assays fall in the middle rectangle, the assays both suggest that heparin anti-coagulation is in the therapeutic range. Values in the discordant areas occur when information provided by the two assays is discrepant (e.g., one assay suggest therapeutic anti-coagulation, whereas the other suggests sub-therapeutic anticoagulation). Thus, our preliminary data in patients with LVADs at our center suggests that the assays are discordant and that there does not appear to be a precise relationship between the assays. In addition to showing discordance, studies have suggested that monitoring heparin with the anti-Xa activity assay may result in lower heparin exposure, fewer dose titrations, lower cost, and possibly less bleeding.[14,15,16,17,18,19,20,21,22,23,24,25,26] Although there have been randomized controlled trials in patients who have not had LVADs or other MCS devices,[17,18] these trials were small, non-blinded, and found no significant differences in bleeding or thrombosis between groups.

Patients who receive LVADs experience a high rate of both thrombotic and hemorrhagic complications in the early postoperative period. Our institution has data for 604 LVADs implanted from 2005 through 2015. A total of 88 patients (14.5%) had suspected pump thrombosis and 164 (27%) had a clinically diagnosed gastrointestinal bleed (Table 1). A substantial proportion of patients develop these complications within 30 days of implant. Since it is likely that insufficient anticoagulation with heparin promotes thrombotic complications, and that overzealous anticoagulation increases the likelihood of bleeding, it is important to identify the impact of heparin monitoring in the perioperative period on these complications. Although some centers have transitioned heparin monitoring from aPTT to anti-Xa, based on biological plausibility and surrogate endpoints, no trials have compared these assays in a rigorous, randomized, comparative effectiveness trial in the perioperative setting.

Utilization of a nursing monitored heparin nomogram with aPTT

Currently, patients receiving IV UFH at our institution are managed with a weight-based dosing nomogram that is monitored and adjusted by nursing utilizing aPTT results. Weight-based heparin dosing nomograms have been associated with a shorter time to achievement of therapeutic anticoagulation compared with empiric dosing by physicians.[27,28] The nursing-driven heparin nomogram was implemented at our institution in 1997 and has been modified over the years in response to data collection and analysis in relation to aPTT targets. A recent survey completed by fifty-six nurses

specialized in post-cardiothoracic surgery care noted 100% satisfaction with the utilization and implementation of our current weight-based heparin nomogram. All nurses noted that the nomogram was clear and easy to follow. Fifty-five (98.2%) nurses felt the current dosing provided in the nomogram is feasible and 53 (94.6%) stated that they follow the dosing and monitoring instructions exactly as they are written. A total of 49 (87.5%) noted that they seek clarification from a co-worker, pharmacist, nurse practitioner, or physician regarding the nomogram instructions. When asked about suggestions for improvement of the nomogram, the most common response was to create a nomogram that is more patient specific for surgical patients at a high risk of bleeding, such as patients with LVADs. These results suggest that implementing a second nomogram based on anti-Xa assay results, that mirrors the same instructions and timing of laboratory draws as the current aPTT-based nomogram, could also be feasible.

Potential Impact of VAD ANTIX

There is much still to be learned in the understanding of bleeding and thrombosis in the perioperative period. Perioperative events can lead to a great deal of variability in pro- and anti-thrombotic hemostatic factor levels.[29] Therefore, the propensity for thrombosis and bleeding in individual patients is frequently unpredictable and, can change substantially over time. Opportunity for discovery is heightened for patients with LVADs, given the dearth of rigorous investigations and the unique features of the human-machine interface. With the recent reports of increasing suspected and confirmed devastating (LVAD) pump thrombosis in the early post-implant period[4], analyses of treatment-related factors such as the method of monitoring anticoagulation are urgently needed. Recent studies in patients with LVADs have correlated factors such as international normalized ratio (INR) in the outpatient setting[30], medication use[31], and elevated systolic blood pressure[32] to pump thrombosis and stroke. However, the impact of monitoring IV UFH therapy with aPTT or anti-Xa in the perioperative period on pump thrombosis, stroke and bleeding remains unknown. The early risk for both bleeding and thrombosis in patients with LVADs underlines the urgency of resolving how best to monitor and achieve appropriate anticoagulation with heparin. Given the ongoing challenges with these competing complications, studying the problem in earnest, while taking into consideration perioperative events, is crucial. Clarifying which of these two monitoring approaches is superior will facilitate safer and more effective anticoagulation with heparin in patients with LVADs.

B Study Objectives

Primary Outcome:

Demonstrate the feasibility and success of implementing nomograms for heparin administration based on both aPTT measurement and anti-factor Xa activity.

Feasibility will be determined by: 1) Questionnaires evaluating the practicality and acceptably of the nomograms 2) The percentage of correct dosing adjustments made by the nursing team required to achieve first therapeutic anticoagulation according to the specified directions provided.

Success will be determined by 1) number of dosing changes required to achieve first therapeutic anticoagulation 2) time (in hours) until achievement of first therapeutic anticoagulation 3) percentage of time therapeutic anticoagulation remains after it is achieved

"Therapeutic anticoagulation" is defined as two consecutive monitoring values within the goal range, according to assigned monitoring assay. (either two consecutive aPTT values within 60-94 seconds or two consecutive anti-Xa values within 0.3-0.7 IU/ml)

Secondary Outcomes:
Explore heparin dosing and the concordance between the aPTT and anti-factor Xa activity in this patient population.

"Concordance" is defined when simultaneously drawn aPTT values and anti-Xas values are within the goal range (aPTT within 60-94 seconds and anti-Xa within 0.3-0.7 IU/ml).

Explore clinical outcomes including pump thrombosis, gastrointestinal bleeding, neurological events such as stroke, and major bleeding in this patient population.

C Study Design

Study setting and design
VAD AntiX feasibility study will take place at Barnes-Jewish Hospital, an academic hospital in affiliation with Washington University Medical Center located in the United States. This trial has been designed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist[33]. The VAD AntiX feasibility study will be a stratified randomized, trial with one specific aim: (1) Demonstrate the feasibility of implementing nomograms for heparin administration based on aPTT measurement as well as anti-Xa activity. This feasibility trial will be the foundation for a larger pilot trial and subsequent comparative effectiveness trial that will seek to determine the optimal monitoring method of IV UFH in the perioperative period for LVAD patients.

A heparin nomogram is a tool or table used to standardized heparin administration and dosing when heparin is administered as a continuous infusion. Dosing adjustments are prescribed in the table based on the laboratory results.

Subject Selection

All patients 18 and older undergoing HeartMate II®, HeartMate III® or HeartWare®, LVAD implantation at Barnes-Jewish Hospital, St. Louis, Missouri, USA will be eligible for enrollment in this study. This hospital is an academic medical center affiliated with Washington University School of Medicine. Patients will be recruited preoperatively and will provide written informed consent. Any patient who is unable to receive heparin [e.g. patients with heparin-induced thrombocytopenia (HIT)] or an anaphylactic allergy to heparin] will be excluded. Patients who develop HIT during the course of the study will remain enrolled and be included in the intention-to-treat analysis.

Inclusion criteria:
All patients 18 years of age and older who are undergoing HeartMate II®, HeartMate III® or, HeartWare® LVAD implantation at Barnes Jewish Hospital, St. Louis, Missouri, USA. Legally acceptable representatives will be able to consent for trial participation.

Exclusion criteria:
Any patient who is unable to receive heparin [e.g. patients with heparin-induced thrombocytopenia (HIT)] or an anaphylactic allergy to heparin] will be excluded. Patients who develop HIT during the course of the study will remain enrolled and be included in the intention-to-treat analysis. Additional exclusions include less than 18 years of age, patients with a known hypercoagulable disorder (factor V Leiden, Antithrombin deficiency, Protein C deficiency, Protein S deficiency, Antiphospholipid antibodies, or other thrombophilia), prisoners, pregnant or lactating women. Also, excluded are patients that are recipients of additional mechanical circulatory support (including extracorporeal membrane oxygenation support, right ventricular assist device, and/or impella) during the index LVAD implantation through the end of the study period.

Recruitment and consent:
Patients will be enrolled during a preoperative clinic visit at our Center for Preoperative Assessment and Planning, from the hospital ward at Barnes-Jewish Hospital, St. Louis, Missouri prior to surgery, or a pre-operative visit at the Ventricular Assist Device Surgery Clinic. Formal consent will be obtained from all participants prior to enrollment in the study. Authorized surrogates will be able to consent for trial participation. Any subject will be free to withdraw their consent at any time.

Interventions
Patients will be randomized to either anti-Xa or aPTT nomograms when the decision is made to start anticoagulation. Patients that receive an additional pumping support device during the index surgery, but prior to randomization will be withdrawn from the study and their baseline data will be discarded. In the rare event the patient receives the assistive pumping device after the index surgery and randomization, they will be withdrawn from the study and the data collected up to that point will be retained for analysis. Consistent with our current heparin management strategy, patients in both arms will be started on a fixed heparin dose (e.g. 750units/hour) on the morning of the first post-operative day. On the second post-operative day, patients will be placed on a

weight-based nursing driven heparin nomogram starting at 12 units/kilogram/hour without a bolus. Patients randomized to aPTT monitoring will follow our institution's current nursing-driven aPTT nomogram and the patients randomized to anti-Xa monitoring will follow a nursing-driven anti-Xa nomogram. Each nomogram has instructions regarding scheduled assay lab draws that nurses will follow. Regardless of group allocation, while IV UFH is administered according to one of the two nomograms, both the aPTT and the anti-Xa activity will be determined at specified time points, although clinicians will only receive the information according to group assignment. Clinicians will be instructed not to deviate from the randomized monitoring protocol. All relevant concomitant care, interventions, and laboratory draws will be at the discretion of the ICU and surgical teams as part of routine postoperative care.

Randomization and Design:
Following LVAD implantation, subjects will be randomized via computer-generated randomization by the study coordinator. Patient randomization will be stratified by LVAD type with HeartMate II®, HeartMate III®, and HeartWare® patients being randomized to the 2 nomograms separately by the assigned study coordinator. Randomization will take place within twelve hours after arrival to the ICU and be subsequent to monitoring and management of heparin anticoagulation with either an aPTT or anti-factor Xa based nomogram.

Subjects in this study will be offered the opportunity to participate in the Systematic Assessment and Targeted Improvement of Services Following Yearlong Surgical Outcomes Surveys (SATISFY-SOS #201203008).

aPTT and anti-Xa Nursing Driven IV UFH Nomograms

aPTT Result	Bolus Dose	Infusion Change
aPTT less than 40 seconds	None	Increase 3 units/kg/hour
aPTT 40-50 seconds	None	Increase 2 units/kg/hour
aPTT 51-59 seconds	None	Increase 1 unit/kg/hour
aPTT 60-94 seconds	None	No change
aPTT 95-104 seconds	None	Decrease 1 unit/kg/hour
aPTT 105-114 seconds	Hold infusion for 30 minutes	Decrease 2 units/kg/hour
aPTT greater than 114 seconds	Hold infusion for 1 hour	Decrease 3 units/kg/hour
Draw STAT aPTT 6 hours after each rate change. Once two consecutive aPTT's are therapeutic (60-94 seconds), then draw aPTT every am. Draw CBC Express every 72 hours until heparin is discontinued.		

Anti-Xa Result	Bolus Dose	Infusion Change
Anti-Xa less than 0.2 IU/mL	None	Increase 3 units/kg/hour
Anti-Xa 0.2-0.29 IU/mL	None	Increase 2 units/kg/hour
Anti-Xa 0.3-0.7 IU/mL	None	No change
Anti-Xa 0.71-0.80 IU/mL	None	Decrease 1 unit/kg/hour
Anti-Xa 0.81-0.99 IU/mL	Hold infusion for 30 minutes	Decrease 2 units/kg/hour
Anti-Xa greater than 0.99 IU/mL	Hold infusion for 1 hour	Decrease 3 units/kg/hour
Draw STAT anti-Xa 6 hours each rate change. Once two consecutive anti-Xa's are therapeutic (0.3-0.7 IU/mL), then draw anti-Xa every am. Draw CBC Express every 72 hours until heparin is discontinued.		

Duration of Study:
Patients will be followed for 14 days of heparin therapy or until heparin has been discontinued (e.g. changed to bivalirudin for anticoagulation or completed a transition to warfarin) if sooner than 14 days. If the patient has not received any IV heparin for 5 consecutive days they will be considered to have failed anticoagulation and the reason noted by the clinical team for discontinuation will be recorded.

The requirement for clinical team training and feedback:
A necessary first step in embarking on this feasibility trial is to train the clinical staff in the use of algorithms for IV UFH administration postoperatively in patients following implantation of the LVAD. It is important first to show that nomograms are practical such that clinicians can easily follow them, and second that by following the nomograms the target parameters are achieved. The collaborators in this study represent the key stakeholders responsible for the management of patients with LVADs in the postoperative period. As such, there is commitment from medical, nursing and pharmacy leadership to manage heparin administration based on either the current aPTT based or the new anti-Xa based nomogram (Table 2). During the feasibility phase, all the medical and nursing staff will undergo structured training in the rationale behind and implementation of the nomograms. Structured training will take place through formal physician and nursing in-services provided by our clinical nurse specialist and clinical pharmacist specialist. The training will include background information, practical advice, mock scenarios, trouble shooting and safety tips. To assess impact, questionnaires for the nurses taking care of the study patients will be handed out by the research team on each nursing shift. The research team will collect the completed forms for input into the database.

Risks and mitigation efforts:
Although the antifactor Xa guided heparin nomogram is standard of care at other institutions, BJH utilizes the aPTT guided heparin nomogram for management of postoperative anticoagulation of LVAD recipients. Given this, the risks to subjects in this

study are associated with randomization to anti-factor Xa guided heparin nomogram for management of anticoagulation therapy postoperatively.

The risks are anticipated to be the same in both arms of the study (anti-Xa guided heparin monitoring or aPTT guided heparin monitoring); namely, increased ease of bruising, increased ease of bleeding, feeling lightheaded, fainting, fatigue, blood in the urine, stool and vomit, gastrointestinal bleeding, mediastinal bleeding, retroperitoneal bleeding, stroke, and LVAD thrombosis. Additionally, there may be other risks such as changes in the frequency of occurrence of these risks when using the anti-factor Xa heparin nomogram that are not yet known.

There is also the possibility of confidentiality breach that could be associated with collection of data from the subject's medical record.

Every subject will receive routine maximum acuity care by clinical teams trained to transition LVAD patients from surgery to heparin anticoagulation and eventually to warfarin therapy. Additionally, study-specific training will be conducted with the clinical teams to ensure correct use of each of the nomograms being compared. All the medical and nursing staff will undergo structured training in the rationale behind and implementation of the nomograms. Structured training will take place through formal physician and nursing in-services provided by our clinical nurse specialist and clinical pharmacist specialist. The training will include background information, practical advice, mock scenarios, trouble shooting and safety tips.

The clinical team has the option of requesting the alternative monitoring test for any study subject (or any other laboratory assay), if they believe more information is required to properly assess the anticoagulation status of the subject. The clinical team also has the option of withdrawing the subject from the study if they feel it is in the best medical interest of the subject. Subjects and their family may choose withdrawal at any time for any reason.

In an effort to protect confidentiality, subjects will be assigned a study specific code that will be linked to their medical record number. The key to this code will be available only to members of the research team and will be stored separately from the study data in a locked cabinet, behind a locked door.

At the conclusion of the study,14 days of heparin therapy or heparin discontinuation if sooner than 14 days, patients will no longer be followed as part of this study; the patients will continue to be monitored and cared for by their clinical team per routine care. These patients may continue to be monitored and data collected as part of the separate SATISFY SOS study. If patients are not co-enrolled in SATISFY SOS, then no further follow-up will take place.

D Study Procedures

Screening and recruitment:
We will identify potential subjects from the Ventricular Assist Device Surgery Clinic, BJH Medical Floors census, surgery schedule or the CPAP Clinic. We may contact them by phone to determine interest in participating. If they are interested, we will arrange to meet with them prior to their scheduled surgery. In order to determine minimum eligibility, we would screen their medical records for their name, date of birth, diagnosis, surgical procedure, current medications, history of heparin-induced thrombocytopenia [HIT], and history of allergic reaction to heparin.

A member of the research team will describe verbally all study components, review the informed consent document, and answers all questions. Potential participants/LARs are informed verbally and in writing that participation is voluntary and they may refuse to participate or may withdraw from the study at any time without penalty.

Nomogram intervention procedure:
aPTT monitoring group: While on fixed-dose heparin (750 units/hr), an aPTT and an anti-Xa will be sent every 6 hours from the same tube (2.7 ml of blood in a light blue top tube). The tube will be sent and processed via standard procedure for the aPTT assay to which the patient is randomized. A paper requisition form and an assigned study ID number will accompany the tube with an order for an anti-Xa that will result in a research profile blinded to the clinical team, but available to the research team. This will be the process for all the subsequent aPTT/anti-Xa lab draws in the aPTT monitoring group. When the clinical team decides to start weight-based heparin dosing, the aPTT heparin nomogram order bundle will be ordered as per standard of care. The process noted above for lab draws and paper requisition forms will apply to the weight-based heparin nomogram as well. The aPTT and anti-Xa will be drawn every 6 hours until two values are in the therapeutic range. Once two values are within the therapeutic range, they will be drawn every 24 hours. All timed lab draws are current standard of care for patients being monitoring on heparin nomograms at BJH.

anti-Xa monitoring group: While on fixed-dose heparin (750 units/hr), an anti-Xa and an aPTT will sent every 6 hours from one tube (2.7 ml of blood in a light blue top tube). Monitoring heparin therapy with this frequency is current standard of care. The tube will be sent and processed via standard procedure for the anti-Xa assay to which the patient is randomized. A paper requisition form and an assigned study ID number will accompany the tube with an order for an aPTT that will result in a research profile blinded to the clinical team, but available to the research team. This will be the process for all the subsequent aPTT/anti-Xa lab draws in the anti-Xa monitoring group. When the clinical team decides to start weight-based heparin dosing (per standard of care), the anti-Xa heparin nomogram order bundle will be ordered. The process noted above for lab draws and paper requisition forms, will apply to the weight-based heparin nomogram

as well. The aPTT and anti-Xa will be drawn every 6 hours until two values are in the therapeutic range. Once two values are within the therapeutic range, they will be drawn every 24 hours. All timed lab draws are current standard of care for patients being monitoring on heparin nomograms at BJH.

Outcomes data

Data collected includes surrogate markers of hemorrhage such as number of blood transfusions and hemoglobin/hematocrit values during IV UFH anticoagulation administration. Surrogate markers of device thrombosis such as lactate dehydrogenase values, haptoglobin values, and device malfunction and/or device power will also be collected. Diagnostic imaging will be reviewed to assess for bleeding and/or thrombotic complications. Once surrogate makers are collected, The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) definitions for LVAD thrombosis, neurologic dysfunction, and major bleeding will be utilized.[34]

As such, suspected LVAD thrombosis will be defined as two of the following three criteria: presence of hemolysis defined as LDH > 1000 IU, presence of heart failure not explained by structural heart disease and/or abnormal pump parameters. Confirmed pump thrombosis will be defined as major pump-related malfunction in which thrombus is confirmed within the blood contact surfaces of device inflow cannula or outflow conduit or grafts.

Neurologic Dysfunction will be defined as a new, temporary or permanent, focal or global neurologic dysfunction ascertained by standard neurologic exam or surveillance neuroimaging. Event should be further subclassified by event types: 1) transient ischemic attach, defined as acute neurologic dysfunction, which resolves in 24 hours and not associated with infarction on brain imaging. 2) ischemic stroke defined as a new acute neurologic deficit of any duration associate with acute infarction on imaging corresponding anatomically to the clinical deficit. 3) Acute symptomatic intracranial hemorrhage, defined as a new acute neurologic deficit attributable to intracranial hemorrhage (ICH). ICH subtype should be specified as one or a combination of subarachnoid, intraventricular, parenchymal, subdural. 4) Clinically covert ischemic stroke or ICH: infarction or ICH seen on surveillance imaging, without conical finding of stroke or ICH at the time of event recognition. 5) Hypoxic-ischemic encephalopathy due to hypoxic-ischemic injury (HIE), manifest as clinically evident signs or symptoms or subclinical electrographic seizures found by complete neurological diagnostic evaluation to be attributable to acute global or focal hypoxic or ischemic brain injury not meeting one of ischemic stroke or ICH events noted above. 6) Acute new encephalopathy due to other cause, manifest as clinically evident signs or symptoms or subclinical electrographic seizures found by complete neurological diagnostic evaluation to be attributable to causes other than stroke, ICH, or HIE.

Major bleeding will be defined as suspected internal or external bleeding resulting in death, re-operation, hospitalization, or transfusion. If transfusion is the metric used to determine major bleeding, must be greater than or equal to four packed red blood cells

within any 24 hours period during the first 7 days postoperatively or after 7 days, a transfusion of packed any red cells will be used and the number transfused noted.

Reporting adverse and serious adverse events
The potential serious risks attributable to avoiding anticoagulation as well as providing heparin and warfarin anticoagulation are well known and include gastrointestinal bleeding, mediastinal bleeding, retroperitoneal bleeding, stroke, LVAD thrombosis, and potentially death. As these are known and anticipated, they will be reported annually to the IRB. All unexpected adverse events associated with research participation or study intervention will be reported to the WUSTL IRB per their Reportable Event Reporting guidelines [WUSTL IRB Policies and Procedures, Section X]. All safety events, including adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations will be reported to the PI in a timely fashion.

The specific monitoring plan for this investigation is commensurate with the risks and the size and complexity of the investigations planned with this feasibility trial. Should there be an unanticipated serious adverse event that potentially increases the risks to the participants, the study will be stopped, an investigation will be conducted by the PI and research team members, and a findings report will be generated and submitted to IRB before the study is resumed. The safety data will be monitored and reviewed every 3 months.

E Statistical Plan

Sample size:
For the planned feasibility study, we have selected a convenience sample of 20 patients; 10 patients randomized to the anti-Xa monitoring arm and 10 patients randomized to the aPTT monitoring arm. Data collected on subjects that were excluded based on receipt of an additional pumping device during the index surgery but prior to randomization will not be included in the dataset. Data from subjects excluded based on receipt of an additional pumping device after randomization will be retained and analyzed up to the point of withdrawal from the study.

No power analysis is planned for this feasibility trial.

Descriptive statistics will be performed looking at the study groups.

For feasibility, questionnaires completed by the nursing staff evaluating the practicality and acceptably of the nomograms will be analyzed with descriptive statistics and compared between the two groups using a Chi square test. The percentage of correct dosing adjustments made by the nursing team required to achieve first therapeutic anticoagulation will be compared between the two groups using a Mann Whitney U test. For success, the number of dosing changes required to achieve first therapeutic

anticoagulation, the time (in hours) to achievement of first therapeutic anticoagulation, and the percentage time therapeutic anticoagulation remains after it is achieved will be compared between the two groups using a Student's t-test if data is normally distributed or a Mann-Whitney U test if data is not normally distributed.

If possible based on population size, concordance between groups of aPTT and anti-factor Xa activity will be assessed with a suitable (parametric or non-parametric) mixed effects statistical model. This approach is likely to yield more accurate information than crude correlation assessments that have been used in other studies, which have not taken into account repeated measures within patients. We will use repeated measures ANOVA and Tukey's test for multiple comparisons to analyze heparin administration in the two groups. With a mixed effects model, we will compare heparin dose in the two groups, while controlling for confounders, including the effect of time on the dose of heparin administered, and assuming an autoregressive covariance structure (the nature of the correlations between measurements for the same patient), as well as a random intercept to allow for some of the effect of potential unknown confounders.

If possible based on study size, markers of gastrointestinal bleeding, major bleeding, neurologic events, and thrombotic complications will be compared with a Chi-square test. Additionally, as able, adjusted logistic regression will be used to explore risk factors for complications. We will use intent-to-treat approach in our analyses. We will also use appropriate imputation methods and test the sensitivity of our results. No imputation is planned for missing primary outcomes data.

F Data Handling and Record Keeping

Data Collection and Methods
All questionnaire's performed will be collected and responses recorded.

At the time of enrollment, detailed patient characteristics and baseline laboratory values will be obtained from the electronic medical record. All patients will have the following laboratory values drawn at baseline (if not already available) and clinicians will have the results readily available: complete blood count (CBC) and complete metabolic panel (CMP) as part of routine patient monitoring. During days 1-7 and 8-14 the lowest hemoglobin, Hematocrit will be collected during each interval. During days 1-7 and 8-14 the highest bilirubin and triglycerides will be collected during each interval. All PT/INR values will be collected during the study.

Surrogate markers of device thrombosis such as lactate dehydrogenase values, haptoglobin values, and device power will also be collected.

Any other operations during the study interval will be recorded as well as the details associate with the operation.

Any endoscopies or evaluations to identify gastrointestinal bleeding, neurologic events, or major bleeding will be recorded.

Additionally, blood will be drawn at randomization, day 2 of heparin, day 4 of heparin, day 8 of heparin and day 12 of heparin (5mL of blood per specimen, with maximum of 25mL). These specimens will only be collected if patient has not completed the intervention (e.g. has not bridged to warfarin). This specimen will be frozen for later analysis to further interrogate the hemostatic system. Thrombin generation will be assessed with the use of a functional thrombin generation assay (TGA) (Technothrombin) on the frozen specimen.

Data Management

A database for this study will be created using REDCap (Research Electronic Data Capture). REDCap uses browser-based software for managing research data. We will have access to REDCap through the Division of Biostatistics and Informatics at Washington University. REDCap servers are securely housed and managed by the Division of Biostatistics. All REDCap data transmission is encrypted following the HIPAA-Security guidelines. Patient safety in this study will be addressed with a comprehensive data safety and monitoring plan that complies with National Institutes of Health guidelines. We plan to produce detailed standard operating procedures for all members of the research team. We also plan to train all members of the research team to take proactive steps to minimize the risk for missing data. Protected health information will only be shared with the research team members

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