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Development of Multidisciplinary Anticoagulation Management Guidelines for Patients Receiving Durable Mechanical Circulatory Support

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Abstract

Patients receiving durable mechanical circulatory support (MCS) require life-long anticoagulation with a vitamin K antagonist (VKA). Due to alternations in hemostasis, concomitant therapy with antiplatelet agents and critical illness, they are at increased risk of thromboembolic and bleeding complications compared with the general population managed on VKAs. To prevent thrombotic events, current guidelines recommend that patients with MCS receive long-term anticoagulation with a VKA to maintain a target international normalized ratio (INR) as specified by device manufacturers, but limited data exist regarding specific routine management of anticoagulation therapy and its potential complications. To optimize anticoagulation management and minimize risk in these patients, we have centralized anticoagulation management in a collaborative approach between the inpatient hemostatic and antithrombotic (HAT) stewardship service and between ambulatory anticoagulation management service (AMS) and the advanced heart disease team. Patients are followed by these three services beginning when the device is implanted and extending the duration that patients have the device. The teams include multiple clinicians from cardiac surgery, cardiology, hematology, pharmacy, nursing, case management, nutrition, and psychiatry, therefore, in order to standardize practice among clinicians without compromising patient centered decision making, we assembled an interdisciplinary team to create multiple treatment guidelines. In addition to a centralized and collaborative approach, our guidelines ensure seamless transitions of care between the inpatient and outpatient settings. We believe our approach has demontrated a positive improvement in the care of these challenging patients. In this article, we present our comprehensive centralized anticoagulation management approach for patients with left ventricular assist systems (LVAS).

Keywords

mechanical circulatory support, ventricular assist device, anticoagulation, thrombosis, bleeding

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Background

Heart failure continues to be a worldwide epidemic, effecting nearly 5.7 million adults in the United States.[1] Mechanical circulatory support (MCS) with left ventricular assist systems (LVAS) has become an established option for patients with advanced heart failure as bridge-to-transplant (BTT), bridge-to-decision, or destination therapy.[2] By the end of 2014, more than 15 000 patients had received an LVAS, at an estimated rate of more than 2000 implants annually across 150 centers in the United States.[3] Although implantation of an LVAS improves prognosis, functional status, and quality

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of life in patients with advanced heart failure, it is also associated with serious complications including thrombotic and bleeding events.[3]

The interaction of the LVAS with the vasculature results in profound hematologic alternations including hemolysis, degradation of von Willebrand factor multimers, platelet activation, and initiation of the coagulation cascade. Managing these imbalances requires indefinite treatment with anticoagulation and antiplatelet agents.[4,5] The physiologic response to the LVAS in combination with antithrombotic agents can lead to significant bleeding and thrombosis-related complications. Rates of these complications vary based on the type of device, patient-specific risk factors, and anticoagulation management, but have been reported as high as 60% for bleeding, 10% for pump thrombosis, and 17% for ischemic stroke at 2 years post-LVAS implantation.[6-8]

Despite the need for indefinite antithrombotic therapy for this growing population of high-risk patients, guidelines for optimal management are equivocal and supported by limited quality evidence including observational studies and expert opinion.[9] Device manufacturers provide recommendations regarding anticoagulation and antiplatelet therapy, but do not provide standardized approaches to achieve and maintain these targets, particularly in those who experience complications.

Vitamin K antagonists (VKAs) such as warfarin are the standard for patients with LVAS due to lack of evidence of safety and efficacy with the direct-acting oral anticoagulants (DOACs).[10] Alternatively, low-molecular-weight heparin (LMWH) and fondaparinux may be used in the outpatient setting; however, limited data exist supporting long-term use of these agents in patients with LVAS. The quality of anticoagulation management is assessed using the time in therapeutic range (TTR). In the atrial fibrillation population, higher TTRs have correlated with improved clinical outcomes.[11] Utilizing a centralized anticoagulation management service has further improved quality management and demonstrated higher TTRs compared with traditional provider-driven management.[12] For patients with LVAS, anticoagulation control is more complicated due to frequent interventions requiring interruption of therapy, infections requiring long-term suppressive therapy with interacting medications, fluctuations in volume status associated with heart failure exacerbations, polypharmacy, and other variables relevant to all patients on anticoagulation. The TTR for patients with LVAS has been historically reported between 31% and 52%, which is significantly lower than in other patient populations.[13-16] A 2017 meta-analysis reported a mean TTR of 46.6% in patients with LVAS.[17] For these reasons, quality anticoagulation control typically targets a TTR benchmark of approximately 50%. Recent data have correlated lower TTRs with higher bleeding and thrombotic rates.[14] One retrospective analysis reported that a TTR greater than 60% in patients with LVAS was associated with less bleeding and fewer thrombotic complications.[15]

In response to the lack of clear guidance and high rates of complications, practice varies widely based on patient and provider experiences. To decrease clinical variation at our institution, we developed a set of practice guidelines specific to antithrombotic management of our patients with LVAS, the Anticoagulation Management of Ventricular Assist System Patients Guideline, which addresses anticoagulation management in 3 phases of care including: (1) perioperative anticoagulation management during the initial hospitalization for LVAS placement, (2) subsequent inpatient admissions, and (3) routine outpatient management. Additionally, we describe our management guidelines for critical complications including bleeding and pump thrombosis. In this report, we describe our services and guidelines and provide a brief overview of the results we have had with this approach.

Methods

Description of Multidisciplinary Team

At our institution, patients with LVAS are followed by the advanced heart disease (AHD)/MCS program that consists of a multidisciplinary team, including cardiac surgery, cardiology, hematology, pharmacy, nursing, case management, and other disciplines as needed such as nutrition, psychiatry, and social work. Anticoagulation therapy is centrally managed in both the inpatient and the outpatient settings by specialized pharmacists from the inpatient hemostatic and antithrombotic (HAT) stewardship service and the anticoagulation management service (AMS), respectively. These teams collaborate on antithrombotic management-related decisions to ensure seamless transitions of care. For full description of these services, refer to the supplemental text.

Anticoagulation Management Quality Assessment

Anticoagulation quality and clinical outcomes data are collected and reported monthly to AMS/HAT leadership and front-line staff as well as quarterly to AHD/MCS leadership and the Pharmacy Credentialing committee, and annually to the Pharmacy and Therapeutics committee. We use 12-month TTR data to assess anticoagulation quality. We calculate the TTR for our entire clinic population as well as the LVAS subpopulation using the centralized electronic anticoagulation management software that utilizes the Rosendaal method and excludes any international normalized ratios (INRs) generated while patients are in a manual (admitted to the hospital or initiation of anticoagulation) or bridging status.[18] Clinical outcomes assessed include critical INRs, major bleeding events, thromboembolic events, heart transplants, deaths, and re-admissions due to anticoagulation-related events within 30 days of discharge postimplantation. Major bleeding events are defined as those requiring hospitalization (gastrointestinal bleed [GIB], intracranial hemorrhage [ICH], hematoma, hematuria, epistaxis, hemoptysis). Thromboembolic events include cerebral vascular accident (CVA), transient ischemic attach (TIA), suspected pump thrombosis, confirmed pump thrombosis, and systemic embolism (venous or arterial thromboembolism).

Institution-Specific Anticoagulation Strategy

As multiple clinicians are involved in patient care, we assembled an interdisciplinary team to create guidelines for practice

Table 1. Inpatient Anticoagulation Management of Patients With Left Ventricular Assist Systems.

Antithrombotic management prior to LVAS placement	
Baseline labs	
Minimum	PT; PTT; INR; platelet count
Additional	Anticardiolipin; lupus anticoagulant; factor V Leiden screen; prothrombin gene mutation; AT3 function; protein C function and protein S[a]
Past medical history	History of VTE or hemorrhage event while on anticoagulation; hypercoagulable disorders
Family history	Hypercoagulable disorders
Medications prior to admission	
Routine LVAS placement	• Aspirin: continue • Clopidogrel: stop 7 days prior to surgery • Warfarin: stop $\geq$4 days prior (goal INR $\leq$1.2) • Direct oral anticoagulants: stop $\geq$48 hours prior based on agent and renal function • If IV anticoagulation required, consider bivalirudin (PTT 60-80) to avoid development of antiheparin PF4 antibodies
Urgent LVAS placement	Consider reversing with IV vitamin K and/or 4F-PCC depending on urgency of procedure
Postoperative LVAS anticoagulation management	
Postoperative day 0 (if patient extubated)	• If $\geq$120 000 platelets/μL start aspirin 325 mg • If <120 000 platelets/μL start aspirin 81 mg
Postoperative day 1	• Initiate aspirin if patient not initiated on POD 0 • Initiate warfarin (max starting dose 4 mg, but decrease based on drug–drug interactions, age, nutritional status, previous warfarin dosing requirements, and post-op hemodynamic stability) • INR range dependent on device
Postoperative day 2	• Initiate *IV anticoagulation* (Appendix A Supplementary material) for a minimum of 5 days and therapeutic INR $\times$ 2 consecutive days • Initial PTT goal 40 to 60 seconds • Titrate to PTT goal 60 to 80 seconds as hemostasis improves
Subsequent inpatient admissions	
• Warfarin managed by HAT • For subtherapeutic INRs, consider bridging with 0.5 to 1 mg/kg bid of enoxaparin, fondaparinux, or IV anticoagulation (see IV Anticoagulation Guideline for Choice of Agent) ○ For new implants (within 3 months) avoid the use of LMWH due to increase bleeding risk ○ For re-admits after 3 months, may choose IV anticoagulation of LMWH • For procedures and surgical interventions consider maintaining the INR within goal and using Kcentra for temporary reversal to maintain consistent anticoagulation vs reversing with vitamin K and bridging postprocedure	

Abbreviations: AT3, antithrombin III; bid, twice daily; HAT, hemostatic antithrombotic stewardship; INR, international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; LVAS, left ventricular assist system; PT, prothrombin time; PTT, partial thromboplastin time; VTE, venous thromboembolism.
[a]Protein C and S will be abnormal if patient is on warfarin.

standardization which still allow for individualized patient-centered medicine. These guidelines were developed in conjunction with the AHD/MCS team. In 2013, the HAT service was developed and began routine inpatient management to provide more complete care of these patients and to capture data associated with the entire process of anticoagulation management. These multidisciplinary guidelines were developed in 2014.

Perioperative Anticoagulation Management

Prior to device placement, certain coagulation labs are recommended during evaluation for LVAS candidacy to identify potential barriers to long-term safe and effective anticoagulation. Such labs may include (but are not limited to) anticardiolipin, lupus anticoagulant, factor V Leiden screen, prothrombin gene mutation, AT3 function, INR, partial thromboplastin time (PTT), as well as proteins C and S. In agreement with the national guidelines for anticoagulation management, we adjust warfarin doses based on individual patient response and do not utilize VKORC1 genotyping routinely.[19,20] In addition to baseline labs, a full history is obtained to identify prior thrombotic and bleeding events along with any family history that may predispose the patient to complications (Table 1). A comprehensive medication list is completed at the time of screening including any anticoagulant or antiplatelet agents that may need to be stopped in the days prior to surgery. This guideline provides direction for preoperative reversal of anticoagulation for both routine and urgent LVAS placement.

The postoperative inpatient management recommendations include antiplatelet and anticoagulation strategies for the early postoperative period. Postoperative anticoagulation is initiated and managed by the HAT pharmacist in conjunction with the

Table 2. Outpatient Anticoagulation Management of Patients With Left Ventricular Assist Systems.

Outpatient anticoagulation management	
Laboratory monitoring	INR: 1 to 2 times weekly by venipuncture only[a] • if TTR >66% may consider q2weeks with MD/NP approval LDH: with clinic visits and as needed
Maintenance	Refer to warfarin maintenance nomogram (Appendix B Supplementary Materials)
Critical high INRs $\geq$0.5 above target range	Refer to critically high INR protocol (Appendix C Supplementary Materials)
Subtherapeutic INRs	Refer to anticoagulation bridging in mechanical circulatory support guideline (previous published)[20]
Routine procedures	Right heart catheterization (RHC): • INR goal <3 • No need to discontinue LMWH or IV DTI of fondaparinux Colonoscopy: • INR goal <3 for colonoscopy (no biopsy) • INR goal $\leq$1.7 with bridge agent when biopsy is likely • Bridging agent should be stopped at least 24 hours prior to procedure
Bleeding events	Consider patient-specific risks when deciding to stop or adjust therapy • First minor bleeding event: decrease aspirin to 81 mg daily • Second minor bleeding event or first major event: hold aspirin and consider a decrease in INR range by 0.5 For GI bleeding, refer to GI bleeding management in LVASs Guideline (Figure 1)
Threatened pump thrombosis	• Admit for bivalirudin (goal PTT 70-90) • Consider increasing aspirin to 325 mg daily and adding dipyridamole 75 mg PO tid if not current regimen • Avoid routine increases to the INR target range
Device-specific INR antithrombotic recommendations	
Device	INR goal range (per IFU) and antiplatelet therapy
Centrimag[b]	INR 2-3, aspirin 325 mg daily
HeartMate II	INR 2-3, aspirin 325 mg daily
HeartMate 3	INR 2-3, aspirin 325 mg daily
HeartWare	INR 2-3, aspirin 325 mg daily
SynCardia TAH	INR 2.5-3.5, aspirin 325 mg daily

Abbreviations: GI, gastrointestinal; IFU, instructions for use; INR, international normalized ratio; IV, intravenous; LDH, lactate dehydrogenase; NP, nurse practitioner; PO, orally; PTT, thromboplastin time; q, every; TAH, total artificial heart; tid, three times daily; TTR, time in therapeutic range.
[a]Point of care (POC) testing is not recommended for patients with VAD.
[b]INR goal may be adjusted based on patient-specific characteristics for thrombosis such as atrial fibrillation, venous thromboembolism, and other hypercoagulable states.

surgical team; however, for LVAS placed on weekends or holidays, initial dosing is done by the cardiac surgery service. To support these providers, the guideline includes considerations for appropriate starting doses based on risk factors for bleeding and warfarin sensitivity (eg, age, liver dysfunction, nutritional status, history of warfarin dosing, drug–drug interactions). Once hemostasis is achieved, it is recommended to start antiplatelet therapy (postoperative day [POD] 0) along with intravenous (IV) anticoagulation as a bridge to a therapeutic INR (typically PODs 1-3; Table 1; Supplementary material Appendix A). The choice of IV anticoagulant and intensity of anticoagulation is based on the patient's transplant status and concomitant comorbidities. Once started on oral anticoagulation with warfarin, standardized device-specific INR goals are provided with a notation that patient-specific factors should also be considered (eg, previous history of stroke, bleeding, presence of mechanical valves, atrial fibrillation, and history of arterial or venous thromboembolism; Table 2). Finally, guidance is provided for patients who require IV anticoagulation with a direct thrombin inhibitor (DTI) due to a history of heparin-induced thrombocytopenia (HIT) or BTT status. We utilize bivalirudin in BTT patients to decrease exposure to heparin and decrease the risk of development of HIT antibodies prior to heart transplant requiring cardiopulmonary bypass (CPB). We reserve heparin for use during CPB given some data suggest that use of bivalirudin while on CPB is associated with a higher risk of early bleeding due to lack of a reversal agent, although there was no difference at 24 hours.[21] Compared to anti-Xa testing, PTT is more sensitive to small changes with heparin. Both lab tests are affected by different patient variables and cannot be correlated with each other. For these reasons, we monitor heparin infusions with the PTT test routinely unless the patient has an elevated PTT at baseline and requires anti-Xa monitoring.[22]

For subsequent inpatient admissions, the guidelines note that anticoagulation is managed by the HAT service. The

guideline also provides information on bridging for subtherapeutic INRs and strategies for managing anticoagulation around procedures and surgical interventions.

Outpatient Anticoagulation Management

For routine outpatient management, the guideline outlines standard INR and lactate dehydrogenate (LDH) testing frequency, gives instructions for when the AHD/MCS team should be contacted and provides links to other LVAS-specific and general anticoagulation-related hospital guidelines including management of critically high and low INRs and strategies for bridging during subtherapeutic INRs.[23] The guideline addresses anticoagulation strategies for specific scenarios such as management of antiplatelet agents surrounding bleeding events and specific recommendations for patients requiring right heart catheterizations or routine colonoscopies. Finally, the guideline provides management recommendations for patients with threatened or confirmed pump thrombosis (Table 2; Supplementary Material Appendix A).

Patients are educated on the importance of anticoagulation, adherence to INR monitoring, the risks of thrombosis and hemorrhage, and factors that influence the INR. Venipuncture is the standard for INR testing in these patients. Point-of-care (POC) INR testing using whole blood from a fingerstick should be interpreted with caution.[24] Certain patient and medication interferences common among patients with LVAS such as anemia, hemolysis, fibrinogenemia, and use of parenteral anticoagulants may reduce the accuracy of POC devices as well as any INR >4 on a POC device.[25-28] The INR is monitored 2 to 3 times weekly until it is stable within therapeutic range for at least 2 consecutive readings. Once the INR is stable, monitoring is done once weekly. In patients with TTR >66%, testing every 2 weeks may be considered but requires discussion and approval by the AHD/MCS team. Warfarin maintenance therapy is managed per the standard institution nomogram (Supplementary Material Appendix B).

Critically high INR results, defined as INR $\geq$4.5, are managed per current national and institution guidelines (Supplementary Material Appendix C).[19,20] Currently, there is no consensus on the optimal management of subtherapeutic INRs in patients with LVAS. For critically low INRs, we have created (and previously published) a detailed guideline and associated workflow to facilitate standardization and communication between all clinicians involved in a patient's care.[23] The recommendations adjust the management strategy for new implants versus those implanted more than 3 months prior to the event. They also provide different recommendations for patients with a history of bleeding or thrombotic events. We generally admit patients with a low INR for IV bridging anticoagulation and hemolysis surveillance within the first 3 months post implant due to higher risk of both bleeding and thrombotic events during this critical time frame.[29,30] For patients implanted more than 3 months prior to the subtherapeutic INR, we use both full dosing and half dose bridging strategies with LMWH to minimize the risk of thrombosis while balancing the risk of bleeding.[31] Fondaparinux is used in patients with a history of HIT, or in BTT patients to decrease exposure to heparin products and possible development of HIT antibodies prior to transplant. Our guideline is based on current literature and expert opinion of our multidisciplinary team. Patients with a history of bleeding are managed with a slightly less aggressive bridging strategy whereas those with a prior thrombotic event have a more aggressive strategy due to risk of recurrence.[32] For patients within 3 months of a bleeding and/or thrombotic event, treatment is individualized and requires collaborative discussion between the AMS and AHD/MCS service. While the risks of pump thrombosis and stroke have been significantly reduced with the HeartMate 3 LVAS, we continue to maintain a vigilant approach to early postoperative anticoagulation in patients receiving this device.[33]

Periprocedural Anticoagulation Management

Recommendations for periprocedural management of anticoagulation varies among institutions and options include continuing warfarin therapy at a lower intensity, withholding warfarin to normalize the INR, initiating IV anticoagulation if INR normalization is required, or using a 4-factor prothrombin complex concentrate (4F-PCC) to temporarily reverse warfarin during the periprocedural period. Anticoagulation is resumed when postoperative hemostasis is achieved and depends on the procedural bleeding risk. We favor maintaining anticoagulation with warfarin and administering a 4F-PCC to temporarily reverse the effects of anticoagulation.[34,35] This strategy lessens the need for preprocedural hospitalization for IV anticoagulation bridging and is generally associated with a faster recovery to the target INR decreasing postprocedural hospitalization days.

Management of Bleeding

Major bleeding events are the most common adverse event within the first 12 months of continuous flow LVAS implantation with 7.79 events/100 patient-months from 2012 to 1014.[8] Gastrointestinal hemorrhage is the most common site of bleeding and can occur in up to 40% of patients with LVAS.[36] After initial management of a major bleeding event, decreasing intensity of the antithrombotic regimen is considered. Our guideline provides recommendations for invasive and observational strategies, including endoscopy, push entereoscopy, or colonoscopy, and if needed video capsule endoscopy, imaging, or a tagged red blood scan as directed by consults from the gastroenterology service (Figure 1). Guidance is provided if full or partial reversal of anticoagulation is needed to perform a procedure. If no source of bleeding is identified, our guideline recommends the provider consider discontinuing the antiplatelet agent, decreasing the INR target, and potentially initiating octreotide, danazol, or thalidomide. Reducing the INR range is reserved for patients with multiple major bleeding events or a single sentinel event. Although minimal supporting literature is available, for recurrent bleeding refractory to the strategies

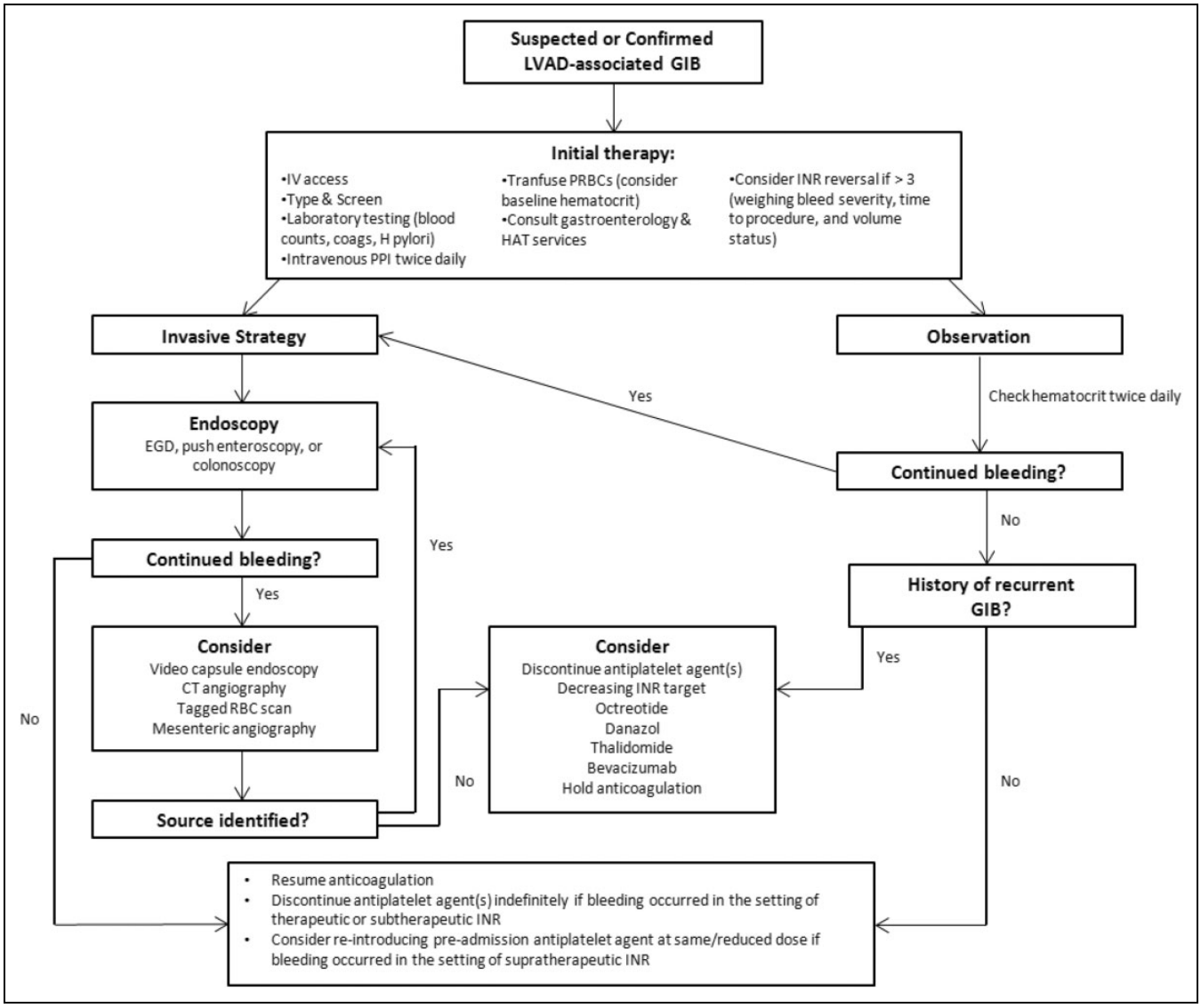

Figure 1. Management of gastrointestinal bleeding in patients with left ventricular assist systems.

above, holding all antithrombotics or trialing bevacizumab is considered (Figure 1).

Management of Pump Thrombosis

Pump thrombosis is a catastrophic event for patients receiving MCS and often leads to death or pump exchange. Kirklin et al reported that the rate of pump exchange or death from definite or probable pump thrombosis at 6 months after implantation increased from 1% before 2011 to 6% in 2012.[37] Most recent data from the MOMENTUM study, however, show a dramatic reduction in suspected or confirmed pump thrombosis with the HeartMate 3 LVAS compared to the HeartMate II device (1.1% vs 15.7% at 2 years, $P < .001$).[33] Patients with signs and symptoms of threatened pump thrombosis, including significantly elevated LDH from baseline coupled with other signs of hemolysis, are admitted and considered for IV anticoagulation until the event is thought to be resolved.[38] Although pharmacologic strategies may resolve initial concerns for pump thrombosis, failure to respond to therapy is quite frequent, and ultimately requires pump exchange.[39] Because of this, our guideline recommends holding warfarin and initiating bivalirudin monotherapy to decrease exposure to heparin products in case the patient requires urgent pump exchange (Table 2, Supplementary Material – Appendix A). We do not recommend the use of thrombolytic therapy due to the high risk of treatment failure or intracranial hemorrhage.[40] If the patient undergoes a pump exchange, the antithrombotic regimen typically remains the same, unless adjustments are required based on the new device implanted or development of new patient-specific risk factors for thrombosis require a change in INR target.

Results

From June 1, 2015, to May 31, 2016, there were 93 patients with LVAS followed by the AMS yielding 996 INR values and

Table 3. Patient With LVAS Population and Demographics.

Baseline Demographics	Patients, n = 93
Age, years[a]	60 (51-67)
Gender (M)	78 (83.9%)
Indication for LVAS	
Ischemic cardiomyopathy	37 (39.8%)
Nonischemic cardiomyopathy	53 (57.0%)
Other	3 (3.2%)
Type of LVAS	
CentriMag	2 (2.2%)
HeartMate II	54 (58.1%)
HeartMate 3	8 (8.6%)
HeartWare	27 (29.0%)
Thoratec PVAD	2 (2.2%)
Implant strategy	
BTT	57 (61.3%)
DT	36 (38.7%)

Abbreviations; BTT, bridge to transplant; DT, destination therapy; LVAS, left ventricular assist system; M, male; PVAD, paracorporeal ventricular assist device.
[a]Median (IQR).

Table 4. Anticoagulation Quality and Clinical Outcomes.

Quality Outcomes	
Average LVAS population TTR (±0.2)	66% (69.4%)
Average TTR target INR range 2-3 (±0.2)	77.8% (82.1%)
Critically low INRs	87 (9.3%)
INRs ≥4	29 (3.1%)
Average time above target range	14.4%
Average time below target range	19.6%
Clinical Outcomes	
Event	Annual risk per patient years
Major bleeding events	
GIB	30.8%
ICH	2.8%
Epistaxis	5.6%
Hematoma	1.4%
Major thrombotic events	
LVAS pump thrombosis	9.8%
CVA	2.8%
TIA	11.2%
Event	Number of patients
Outcomes	
Heart transplant	10 (10.8%)
Death	12 (12.9%)
Time to Therapeutic INR	
Admission reason	Time to therapeutic INR (days)[a]
New LVAS implant	6.3
Bleeding	5.9
Suspected LVAS thrombosis	5.9
All others	3.2

Abbreviations: CVA, cerebrovascular accident; GIB, gastrointestinal bleed; ICH, intracranial hemorrhage; INR, international normalized ratio; LVAS, left ventricular assist system; TIA, transient ischemic stroke; TTR, time in therapeutic range.
[a]Day 1 is day after first dose of warfarin.

24 286 days of follow-up. Baseline demographics are shown in Table 3. Patients were a mean age of 57 years, 83.9% were male, and 61.3% were BTT status. Most patients had a HeartMate II device (58.1%) followed by HeartWare (29.0%) and HeartMate 3 (8.6%). Clinical and quality metrics are shown in Table 4.

The average TTR for all patients with LVAS during this timeframe was 66%. The average TTR for patients with LVAS with a target INR range of 2.0 to 3.0 was 77.8%, with TTR ±0.2 was 82.1%. In total, 87 (9.3%) INRs were critically low and 29 (3.1%) INRs were 4.0 or above. Eight (0.9%) INRs were ≥5.0 and there were no INRs above 10.0. Average times above and below range for all patients with LVAS were 14.4% and 19.6%, respectively.

There were 32 major bleeding events (6 ICH; 21 GIBs; 4 epistaxis; 1 hematoma) and 18 thrombotic events (7 pump thromboses; 2 CVAs; 8 TIAs). Additionally, there were 12 cases of suspected pump thrombosis. Intracranial hemorrhage was observed in 4 patients (3 patients with HeartMate II, 1 of which had 2 separate ICH events; 1 patient with HeartWare having 2 separate ICH events). Death occurred in 2 patients post-ICH. Pump thrombosis and suspected pump thrombosis were primarily observed in those with the HeartMate II (4 of 7 confirmed pump thrombosis and 11 of 12 suspected pump thrombosis). For patients with pump thrombosis, 2 patients received heart transplant and 5 had LVAS exchange. Ten patients received a heart transplant during this time frame and there were 12 deaths.

For inpatient anticoagulation management, the time to therapeutic INR was retrospectively tracked and included the number of days starting with the day after the first dose of warfarin and ending the day of the first therapeutic INR. From June 1, 2015, to May 31, 2016, there were 71 admissions. Time to therapeutic INR was calculated separately based on the reason for admission (Table 4). Warfarin for new patients with LVAS was typically started POD 1 and slowly titrated up to determine patients' warfarin requirements. Dose stacking was minimized to balance the effects of interacting medications and need for possible upcoming procedures. Whether a patient was admitted for an LVAS implant, bleeding, or suspected LVAS thrombosis, the time to a therapeutic INR was on average achieved in 6 days. In those with other reasons for admission (eg, infection), therapeutic INR was achieved much quicker.

Discussion

Robust guidelines do not exist for anticoagulation in patients with LVAS and due to the complex nature of their altered physiology and presence of artificial surfaces, guidelines for management of patients with other thromboembolic disease states cannot be extrapolated. The present article summarizes our detailed and standardized approach for comprehensive anticoagulation management of these patients. It incorporates evidence and expert opinion. The AMS has been responsible

for outpatient anticoagulation management for over a decade. Compared to the commonly published benchmark TTR of 50% in this population, our patients had a 32% increase in the mean TTR with approximately 12% of the time spent in critical ranges. We believe that this is a positive improvement in the management of these challenging patients and is likely reflective of our approach.

Several limitations to these guidelines exist. First, literature used to develop these guidelines consists predominantly of patients with LVAS. While most of our patients have LVAS, we have extrapolated these data to our patients with right ventricular assist systems and biventricular assist systems as well. Second, expert opinion and individual physician experience and preference that influenced these guidelines is representative of a single center and may not represent all physician and institutional philosophies. Third, a comparator arm was not feasible as prior to implementation of the HAT service, inpatient anticoagulation management data were not documented in a centralized system; thus, information prior would have reflected outpatient management only. Additionally, technological advances between 2015 and 2016 have included the HeartMate 3 LVAS, which has decreased the occurrence of ventricular assist device thrombosis admissions. Finally, as new literature becomes available, particularly with new devices or with DOACs, continuous maintenance of these guidelines is required. Collaboration of data collected across multiple institutions would be useful in defining best practices in the future.

Conclusion

It is well documented that MCS patients require tight management of their anticoagulation to safely balance the increased risk of bleeding and thrombosis. Additionally, these patients interact frequently with many different health-care providers during various transitions of care throughout the health-care system. This manuscript presents a unique strategy for utilizing a centralized anticoagulation management approach including a multidisciplinary team that integrates the inpatient to outpatient realms, standardizes practice guidelines, and centralizes documentation and reporting of all anticoagulation-related events and quality metrics.

Authors' Note

Amy A. Levesque, PharmD, Andrea R. Lewin, PharmD, Jessica Rimsans, PharmD, and Katelyn W. Sylvester, PharmD, equally contributed to this work.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Jean Connors is a consultant for Abbott, Bristol Myers Squibb, and advisory board for Boehringer Ingelheim Scientific. Katelyn Sylvester has participated on a scientific advisory board for Bristol Meyers Squibb/Pfizer. Mandeep Mehra is a consultant for Abbott, Medtronic, Johnson & Johnson, NuPulseCV, Mesoblast, Stealth BioTherapeutics, and Portola. The remaining authors have no conflicts of interest to disclose.

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Supplemental Material

Supplemental material for this article is available online.

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