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Original Research

Predicting Bleeding and Thrombosis Complications in Patients with Continuous Flow Left Ventricular Assist Devices

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Abstract

Background

Left ventricular assist device (LVAD) therapy has been proven to relieve heart failure symptoms and improve survival, but is not devoid of bleeding and/or thrombotic complications. Risk stratification tools have been utilized in other cardiovascular disease populations to estimate the risk of bleeding and thrombosis with and without anticoagulation, including the HAS-BLED, HEMORR$_2$HAGES, CHADS$_2$ and CHA$_2$DS$_2$-VASc models. The study objective was to evaluate the predictive value of available risk models for bleeding and thrombotic complications in patients with an LVAD within one year of implantation.

Methods

This was a retrospective, single-center analysis of patients implanted with the HeartMate II continuous-flow LVAD from July 2011 to June 2016. All patients who received an LVAD within the study period were eligible for inclusion. The primary

endpoint was the first occurrence of bleeding or thrombosis within one year from implantation. Baseline risk model scores were calculated at the time of LVAD implantation. Chi-square and student's t-test were used to measure baseline differences and compare mean risk model scores between patients who had an event. A receiver operator characteristic (ROC) curve analysis was performed to evaluate the accuracy of the risk models to predict an event.

Results

A total of 129 patients underwent LVAD implantation within the study time period. Mean $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores were not significantly different in patients with and without an event. The mean $HEMORR_2HAGES$ score was 3.09 and 2.51 in those with and without a bleeding event, respectively ($p = 0.008$). The ROC curve area for the $HEMORR_2HAGES$ model was the highest at 0.620.

Conclusions

The HAS-BLED, $HEMORR_2HAGES$, $CHADS_2$and CHA2DS2-VASc risk stratification models did not accurately predict bleeding or thrombosis events in our population. The mean $HEMORR_2HAGES$ model score was higher in patients who experienced a bleeding event. However, this model did not have strong positive predictive value. Better risk models are needed to predict bleeding and thrombotic events in this patient population.

Keywords: left ventricular assist device, gastrointenstinal bleed, thrombosis, HAS-BLED, $HEMORR_2HAGES$, $CHADS_2$and CHA2DS2-VASc

Introduction

Mechanical circulatory support (MCS) continues to be an essential management strategy for patients with acute or chronic cardiac or pulmonary failure. In patients with advanced heart failure (HF), the implantable left ventricular assist device (LVAD) significantly reduces mortality compared to medical therapy in patients awaiting transplantation (bridge-to-transplant) and those deemed ineligible (destination therapy) (1). According to the Eighth Annual INTERMACS report, there were 22,866 patients implanted with an FDA-approved MCS device from June 2006 to December 2016 (2). Although LVAD therapy has been proven to relieve HF symptoms and improve survival (1), the implantation of an LVAD increases a patient's risk for bleeding and/or thrombotic events (3,4). Conversely, there are a reported 7810 bleeding events per 100 patient-months within the first three months of implantation (2). Arterial non-central nervous system thrombosis, venous thrombosis, and stroke have been reported as 162, 663, and 1162 events per 100 patient-months within the first three months of LVAD implantation, respectively (2). Unfortunately, there are no validated methods to aid in predicting patients at a higher risk for such events.

Risk stratification tools have been utilized in other cardiovascular disease populations to estimate the risk of bleeding and thrombosis with and without anticoagulation, including the HAS-BLED, HEMORR$_2$HAGES, CHADS$_2$, and CHA$_2$DS$_2$-VASc models (5-8). In an effort to limit the devastating complications following LVAD implantation, the previously validated risk models were recently evaluated in LVAD patients. Koene, et al evaluated the HAS-BLED and CHA$_2$DS$_2$-VASc models with outcomes to determine their predictive abilities. The results demonstrated that both models were associated with greater risks of bleeding and thrombotic events, respectively (9). In a later study by Kemal, et al, there was a significant association between elevated HAS-BLED scores and bleeding outcomes, but there was not an association between the CHA$_2$DS$_2$-VASc model and thrombotic outcomes (10). Due to these conflicting results and the limited data in this area, further investigation is warranted to better define methods for predicting complications in these high-risk patients. Additionally, the CHADS$_2$ and HEMORR$_2$HAGES risk stratification tools have not been studied in the LVAD population. The aim of this study was to investigate the predictive value of the HAS-BLED, HEMORR$_2$HAGES, CHADS$_2$, and CHA$_2$DS$_2$-VASc predictive models for bleeding or thrombotic complications in patients with LVADs.

Methods

This was an IRB-approved, retrospective, single-center analysis of patients implanted with a continuous-flow LVAD (CF-LVAD) from July 1, 2011 to June 30, 2016. All patients who received an LVAD in this timeframe were eligible for inclusion. Exclusion criteria were defined as patients with a known clotting disorder, less than 18 years of age, pregnancy, and prisoners. The primary endpoint was the incidence of bleeding and/or thrombosis events up to one year after implantation. Baseline risk model scores were calculated utilizing the previously described HAS-BLED, HEMORR$_2$HAGES, CHADS$_2$, and CHA$_2$DS$_2$-VASc models at time of implantation (5-8). Bleeding events included gastrointestinal (GI) bleeding, intracranial bleeding, and other non-surgical bleeding. Perioperative bleeding (any bleeding occurring within 48 hours of implantation) was not defined as an event. Targeted chart review for bleeding events was conducted on the basis of the thrombolysis in myocardial infarction (TIMI) criteria for minor bleeding (hemoglobin drop ≥ 3 g/dL) during admission and/or the administration of medications for urgent reversal of bleeding (factor VIIa, four factor prothrombin complex concentrate, vitamin K, desmopressin, octreotide, proton pump inhibitor continuous infusions, and/or danazol) based on medication administration records (11). Thrombosis events were defined based on the development of pump thrombosis, ischemic stroke, and/or systemic emboli. Chart review for thrombotic events was performed using medication administration records for alteplase and based on laboratory abnormalities suggestive of pump thrombosis, including lactate dehydrogenase (LDH) ≥ 3x upper limit of normal and plasma free hemoglobin (pfHgb) ≥ 40 g/dL (12). All bleeding and thrombotic events were confirmed utilizing radiographic evidence, laboratory markers, medication administration records, daily progress notes, and discharge summaries. All patients were censored at time of first event, transplantation, death, or at one year post-implantation. Patients were initiated and maintained on institution-specific antithrombotic therapy at time of discharge, including warfarin and an antiplatelet in many circumstances.

A student's t-test was used to compare mean risk model scores between patients with and without an event. A receiver operator characteristic (ROC) curve analysis was performed to evaluate the accuracy of the risk models to predict an event.

Results

A total of 125 patients met inclusion criteria from July 1, 2011 to June 30, 2016. The median age at time of implantation was 54 years (range 18 - 81 years). The mean and median HAS-BLED, HEMORR$_2$HAGES, CHADS$_2$, and CHA$_2$DS$_2$-VASc model scores are presented in Table 1. The majority of patients were Caucasian (90.4%) and male (81.6%). Of 125 patients, 34 patients (27.2%) experienced a bleeding event and 19 patients (15.2%) experienced a thrombotic event. Of the 34 patients with bleeding events, the following events were reported: GI bleed (n = 22), hematuria (n = 3), intracranial hemorrhage (n = 8), or other bleed (n = 6), with five patients experiencing bleeding at two different sites. Thrombotic events included pump thrombosis (n = 9), deep vein thrombosis/pulmonary embolism (n = 4), ischemic stroke (n = 4), or other (n = 2). Seven of the bleeding and thrombosis events that occurred were associated with admission to the hospital and ultimately contributed to inpatient mortality. Median time to bleeding event was 93 days; median time to thrombotic event was 67 days.

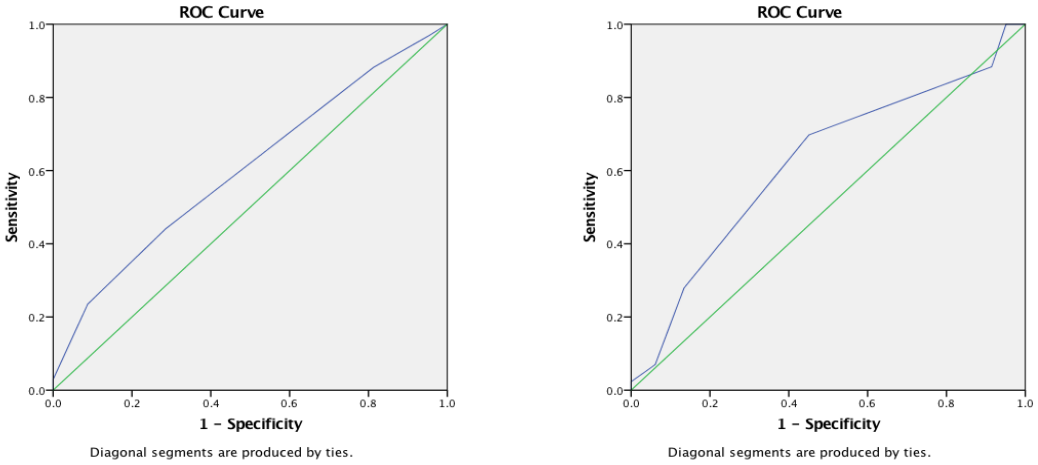
Table 1. *Baseline Characteristics*

Baseline Characteristics (n = 125)		
Variable		**Number of Patients**
Male		102 (81.6%)
Caucasian		113 (90.4%)
Median Age at Implantation (years)		54
Hypertension		102 (81.6%)
Heart Failure		125 (100%)
Diabetes		60 (48%)
Prior History of Stroke or Transient Ischemic Attack		8 (6.4%)
Vascular Disease		73 (58.4%)
Renal Disease		32 (25.6%)
Liver Disease		6 (4.8%)
Alcohol Use		6 (4.8%)
History of Malignancy		11 (8.8%)
Antiplatelet Use		104 (83.2%)
History of Bleed		5 (4%)
Baseline Anemia		52 (41.6%)
Risk Stratification Tool	**Mean (Stdev)**	**Median (Range)**
HAS-BLED	2.26 (0.99)	2 (0 – 5)
HEMORR$_2$HAGES	2.66 (1.11)	3 (0 – 6)
CHADS$_2$	2.47 (0.87)	2 (1 – 5)
CHA$_2$DS$_2$-VASc	3.39 (1.24)	3 (1 – 6)

Table 2. *Bleeding scores and bleeding events*

Primary Outcomes			
	No Bleeding Event n = 91 (stdev)	**Bleeding Event** n = 34 (stdev)	**P - Value**
HAS-BLED	2.14 (0.93)	2.56 (0.19)	0.056
HEMORR$_2$HAGES	2.51 (0.11)	3.09 (0.20)	0.008
CHADS$_2$	2.47 (0.87)	2.47 (0.86)	0.991
CHA$_2$DS$_2$-VASc	3.32 (1.24)	3.59 (1.26)	0.283
	No Thrombotic Event n = 106 (stdev)	**Thrombotic Event** n = 19 (stdev)	**P - Value**
HAS-BLED	2.25 (1.00)	2.26 (0.99)	0.973
HEMORR$_2$HAGES	2.66 (1.07)	2.68 (1.34)	0.932
CHADS$_2$	2.46 (0.84)	2.53 (1.02)	0.768
CHA$_2$DS$_2$-VASc	3.40 (1.25)	3.37 (1.26)	0.929

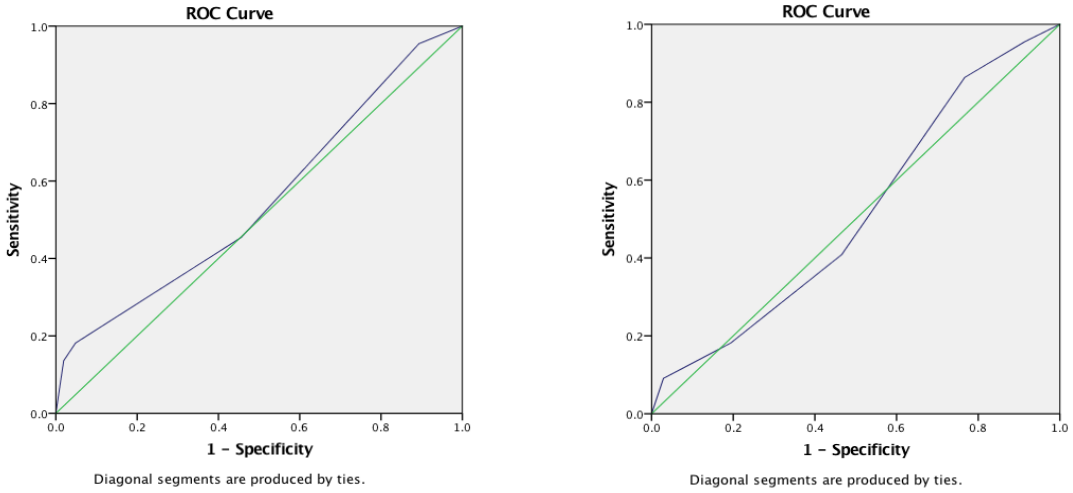
The mean HEMORR$_2$HAGES score was higher in patients who suffered a bleeding event at 3.09 vs patients who did not at 2.51 (p = 0.008). However, there was no statistically significant difference in mean HAS-BLED scores: 2.14 vs 2.56 (p = 0.056) (Table 2). ROC for the HAS-BLED and HEMORR$_2$HAGES risk models showed a weak correlation between scores and bleeding outcomes (Figure 1).



A **B**

Figure 1: (A) *HAS-BLED ROC curve with area under curve (AUC) of 0.603, standard error 0.059, and asymptotic significance value of 0.076.* ***(B)*** *HEMORR$_2$HAGES ROC curve with AUC of 0.620, standard error 0.054, and asymptotic significance value of 0.028. For both graphs, there is little correlation between risk stratification tool and bleeding events seen.*

The mean $CHADS_2$ and CHA_2DS_2-VASc scores were not statistically significantly different for patients who had a thrombotic complication (Table 2). ROC curves were similarly not correlated with thrombotic complications (Figure 2).



A **B**

Figure 2: (A) *$CHADS_2$ ROC with AUC of 0.548, standard error 0.071, and asymptotic significance value of 0.482.* ***(B)*** *CHA_2DS_2-VASc ROC with AUC of 0.513, standard error 0.065, and asymptotic significance value of 0.843. For both graphs, there is no relationship seen between increasing scores and thrombotic events.*

Discussion

In our study population, 42.4% of all patients suffered either a bleeding or thrombotic complication within the first year following LVAD implantation. Despite the high incidence of events in this population, the $HEMORR_2HAGES$ score was the only risk stratification tool to find a statistically significant difference between patients who did and did not suffer a bleeding event. However, further ROC curve analysis did not show strong correlation with higher scores, suggesting that the $HEMORR_2HAGES$ score does not provide an accurate estimation of patients who are likely to suffer a bleeding event. This finding also highlights the complex pathophysiology of bleeding events in this population and the need for further identification of risk factors contributing to bleed outside of the risk stratification tools analyzed in this study.

Despite substantial improvements in the management of HF with CF-LVADs, complications with potentially devastating sequelae remain prevalent. An important next step in LVAD therapy would be to limit the number of these complications or to establish a better modality to predict and prevent adverse events in at-risk patients. However, the mechanism of increased bleed risk is proposed to be multifactorial, making it challenging to implement a one approach to limit bleeding

complications. Specifically, the mechanical shear stress induced by the LVAD may lead to uncoiling of von Willebrand multimers, resulting in increased proteolysis by ADAMTS13 and subsequent development of acquired von Willebrand disease. Additionally, the non-pulsatile nature of CF-LVADs may lead to the development of angiodysplasia and arteriovenous malformations (AVMs). The development of AVMs is particularly common within the GI tract as a result of decreased pulse pressure. Similar to the pathophysiology of bleeding, several mechanisms of thrombosis have been hypothesized including: inorganic material exposure leading to clotting cascade activation, the mechanical shear stress of the device leading to platelet damage and hemolysis/inflammation, and various pump-related risk factors (continuous-flow vs pulsatile flow; centrifugal vs axial) (13-15).

In the MOMENTUM 3 trial, the HeartMate^{TM} 3 centrifugal-flow device (Abbott) was associated with greater event-free survival (alive and free from disabling stroke and emergent pump replacement due to complications) (76.9%) as compared to the HeartMate II axial-flow device (Abbott) (64.8%) at 2 years ($P < 0.001$) (15). Pump thrombosis, stroke, and bleeding complications were also lower in the HeartMate 3 cohort, reinforcing the importance of pump-related factors in coagulopathy and thrombosis risk (15). These numerous factors complicate the determination of risk for each patient, since patients may have differing hematologic responses to the implantation of an LVAD. Despite these differences, many institutions have adopted a standard approach to implementing antithrombotic therapy, often including the use of antiplatelet therapy (aspirin 81-325 mg/day) and warfarin with variable patient-specific international normalized ration (INR) goals. Beyond the mechanistic factors that the LVAD contributes, antithrombotic therapy further complicates the hemostatic picture, creating a difficult balance between bleeding and thrombotic events for these patients.

The incidence of bleeding and thrombotic events in this study (27.2% and 15.2%) was similar to the studies by Koene (24.9% and 12.7%) and Kemal (22.1% and 15.2%) (9, 10). Though both studies examined baseline risk stratification tool scores prior to LVAD implantation, the previous finding that HAS-BLED and CHA_2DS_2-VASc correlates with bleeding and thrombotic outcomes was not replicated in our study population. There are several notable differences that may contribute to the conflicting results among the evaluated studies. In the study by Koene, et al, no patients were documented as having hypertension in the HAS-BLED risk tool compared to 81.6% in the present study. Additionally, while labile INR was included in the study by Koene, et al, only 24.9% of the patient population had INR data available. The current study did not incorporate labile INR into baseline calculations due to inconsistent documentation and the controversy in the best method for calculating time in therapeutic range. There are limitations to excluding labile INR history, since the HAS-BLED score initially included this for prediction of bleeding events up to one year (7). However, withholding the incorporation of pre-implantation labile INRs minimizes the assumption that patients will continue to have labile INRs post-implantation. Drawing further comparisons to previous investigations, the study by Kemal and colleagues included mostly patients implanted with the HeartWare® device (HVAD, Medtronic) and only 21.5% with the HeartMate II device (10). As discussed previously, the device plays a significant role in the etiology of bleeding and clotting in these patients, and differences in device type and function may change

the likelihood of either event occurring. These two different devices did not have significantly different number of thromboembolic events, but nearly all of the bleeding events occurred in the HVAD group (30 of 32 events), meaning that the finding that HAS-BLED scores predicted outcomes in this study was mostly driven by patients with HVAD. As a result of study heterogeneity and differences in institutional practices, it is difficult to derive conclusions regarding the use of these risk stratification tools for all patients receiving a CF-LVAD and highlights the difficulty in achieving strong external validity in this patient population.

Despite the findings in the study by Koene, et al, there remains little investigation into the application of risk stratification tools and prospective interventions into antiplatelet/anticoagulant management. Most modifications to a patient's regimen occur secondary to an identified event and/or history of hemorrhagic or thromboembolic events. Knowing the significant morbidity, mortality, and cost of treating these complications, there remains a large unmet need for better predictive models to limit these adverse events. Koene and colleagues stratified patients into high (≥ 3) and low risk (< 3), suggesting that this can be an approach to assigning patients to different management strategies. However, the results of their study have not been consistently replicated, and there have not been prospective trials evaluating this method. In a more recent study, a predictive model for the risk of GI bleed was created from retrospective outcomes data up to 3 years after LVAD implantation. This model incorporated age > 54 years, history of previous bleed, coronary artery disease, chronic kidney disease, severe right ventricular dysfunction, mean pulmonary arterial pressure (MPAP) < 18 mmHg, and glucose > 107 mg/dL. Patients assigned into low risk (0-1 points), intermediate risk (2-4 points), and high risk (5-9 points) had 3-year GI bleed risks of 4.8%, 39.8%, and 83.8%, respectively [16]. While still lacking prospective confirmation of these results, this tool may better identify a patient's risk for GI bleed, specifically. However, this study did not propose specific interventions to reduce the risk of bleed and did not assess thrombotic complications, which must be carefully balanced before using this algorithm to modify antithrombotic therapy.

A limitation of this study includes its retrospective nature, as our study was restricted to documentation obtained from the electronic health record. Also, as previously discussed, labile INR was not represented in this study and warrants further investigation in the use of various time-in-therapeutic range calculators and outcomes specifically for patients with LVADs. The role of continuously reassessing risk, and at which frequency to do so remains unclear, as all approaches have assessed a baseline risk stratification tool score to predict future outcomes. Because this retrospective analysis occurred in a single institution with a single type of LVAD, the external validity must be interpreted with caution. However, the inconsistent results compared to previous single-center studies highlights the need for large, multi-center studies to evaluate risk factors for developing bleeding and thrombotic events, which may be achieved through the INTERMACS database and collaboration between multiple institutions to achieve better outcomes in these patients. Additionally, the collaboration between multiple centers may allow for the identification of a certain incidence of hemorrhagic and thromboembolic complications that is deemed 'actionable' to modify the patient's antithrombotic regimen post-implantation. A common approach to modify a patient's regimen may be to decrease or increase a patient's INR range for

warfarin management, but the specific modification based on an 'actionable' level of risk of bleeding or clotting still requires further investigation.

Conclusion

Current commonly used risk stratification tools lack consistency in accurately predicting bleeding and thrombotic complications in patients with CF-LVADs. The inconsistency in results between centers suggest that a larger, multi-center study is necessary to confirm these findings. Additionally, further analysis into individual risk factors and development of a unique scoring system may provide helpful information into the initial management of patients being implanted with an LVAD, allowing for a decrease in complication rates due to bleeding and thrombosis. However, further work is warranted to identify specific patients that require modification of antithrombotic therapy and the specific modifications that are needed.

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