Comparative Effectiveness and Economic Evaluations of Anticoagulation Strategies in Patients with Left Ventricular Assist Devices

by

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Abstract

Left ventricular assist devices (LVADs) are surgically implanted devices that support the circulation system in patients with advanced heart failure. Patients with LVADs often require bridging anticoagulation in the chronic therapy phase following hospital discharge to prevent life-threatening thromboembolic complications. Given a lack of clinical trial data and clinical management guidelines, bridging practice varies widely between different LVAD centers. This dissertation evaluated the comparative effectiveness and cost-effectiveness of outpatient management with low-molecular-weight heparin (LMWH) vs hospitalization with unfractionated heparin (UFH) for LVAD patients. We also quantified the potential value of a new trial assessing the relative safety and efficacy of these alternative bridging anticoagulation strategies and determined the optimal design of such a trial.

To assess the comparative effectiveness of LMWH vs UFH bridging, we conducted a retrospective cohort study of adults with LVAD implantation between January 2014 and December 2018 from two academic medical centers. Data were collected from 269 patients and 1364 bridging episodes where either UFH or LMWH was administered. Records were reviewed for 30 days after bridging UFH or LMWH was discontinued, assessing for bleeding and/or thromboembolic events. Multivariable logistic regression analysis adjusted for site- and patient-level clustering along with LVAD type and the HAS-BLED score for bleed risk. We found that the rate of major bleeding or thromboembolism was non-statistically significantly lower for patients receiving LMWH as compared to UFH.

We then projected health and economic outcomes for LMWH vs UFH bridging strategies using a decision analytic model parameterized using data on rates of bleeding and thrombotic events and deaths from our retrospective cohort study of LVAD patients and the published literature. The primary outcome was the incremental cost-effectiveness ratio in 2021 US dollars per quality-adjusted life year (QALY) gained. Using a healthcare sector perspective, the base-case cost-effectiveness analysis showed that outpatient management with LMWH was cost-saving. In probabilistic sensitivity analyses, LMWH remained cost-saving in 98.0% of iterations at a willingness to pay of $100,000/QALY.

Finally, expected value of perfect, partial perfect and sample information (EVPI, EVPPI and EVSI) analyses were conducted using a probabilistic model and the probabilities of bleeding and stroke associated with LMWH and UFH bridging for low INR from a retrospective cohort study examining the 3-month follow-up period after LVAD implantation. EVSI was quantified with net monetary benefit (assuming willingness to pay for health as $100,000/QALY). We calculated discounted population-level EVSI by multiplying per-episode EVSI by the annual number of bridging procedures in the United States and assuming a 10-year time frame over which improved anticoagulation would be used. Study costs were based on administrative costs and LMWH/UFH costs. The discounted population-level EVPI and EVPPI were $5.6 million and $2.8 million, respectively. The VOI from future trials collecting data on adverse event rates was outweighed by the costs of these trials across study sample sizes.

In conclusion, using data on adverse event rates associated with LMWH vs UFH bridging from our retrospective cohort study, we found that there appears to be little uncertainty that outpatient management with LMWH is cost-saving for LVAD patients, as compared to inpatient UFH bridging. Despite the statistical uncertainty in the adverse events associated with the

bridging strategies, a trial in which more information on the relative safety and efficacy of LMWH vs UFH bridging anticoagulation is collected would not represent good value for information.

Chapter 1 Introduction

Heart failure places a heavy burden on society, with an estimated prevalence of more than 5.8 million patients in the United States and over 23 million worldwide [1]. In the United States, the lifetime risk of developing heart failure is one in five, and roughly 300,000 deaths annually are directly attributable to this syndrome. The total cost of care (direct and indirect costs) for heart failure is estimated at $43.6 billion annually [2]. Medical therapies for chronic heart failure are limited, and many patients require heart transplant. Due to a limited supply of donor hearts, utilization of left ventricular assist devices (LVADs) has risen in this population [3].

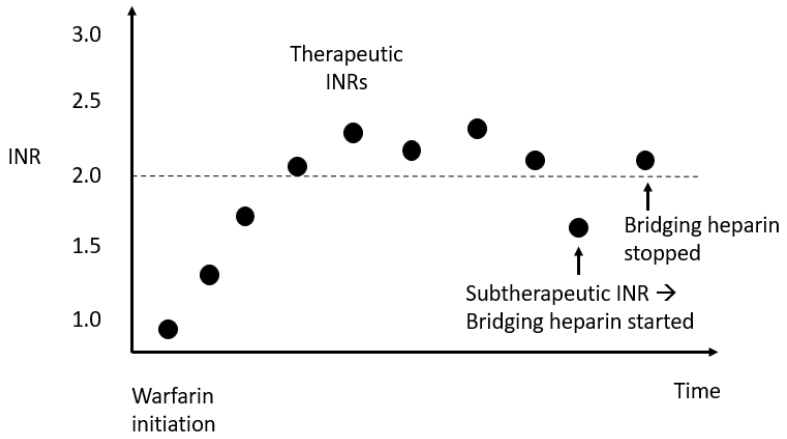
LVADs are surgically implanted devices that support the circulation system in patients with advanced heart failure, either as bridge to cardiac transplant or as destination therapy for patients ineligible for transplant [4,5]. With rapid technological advances made, survival on LVADs has improved substantially. Correspondingly, there has been a sharp increase in the use of LVADs, with over 22,000 left ventricular assist devices implanted in patients with advanced heart failure in the last decade. Current estimates report an annual LVAD implant volume of more than 3,000 in the United States [6].

Yet, LVADs are mechanical pumps that can thrombose, and without appropriate anticoagulation therapy, patients with these devices are at very high risk for life-threatening thromboembolic complications, such as ischemic stroke, systemic embolism, or pump thrombosis [6]. To prevent such complications, all patients using an LVAD are treated with

warfarin anticoagulation, with a target international normalized ratio (INR) range of 2.0 - 3.0 [7,8]. INR is a test that is used to assess a patient's risk of bleeding or the blood's ability to clot [9].

LVAD patients tend to have worse warfarin control than non-LVAD patients, often spending half or more of their time with low INR values (INR < 2.0), placing them at risk for thromboembolic complications [10-12]. Therefore, LVAD patients require the use of a temporary "bridging" anticoagulant until INR is therapeutic (Figure 1.1).

Figure 1.1 Bridging for unexpectedly low INR



Bridging strategies for subtherapeutic INR include outpatient treatment with low molecular weight heparin (LMWH) and intravenous unfractionated heparin (UFH) therapy. UFH is the more costly and less convenient option. While LMWH can be administered once or twice a day as a subcutaneous injection, unfractionated heparin requires hospitalization for intravenous administration.

Given a lack of clinical trial data on the safety of LMWH vs UFH therapy, bridging practice for low INR values varies widely between different LVAD centers. While some LVAD

centers routinely use outpatient LMWH bridging, others hospitalize their patients for UFH bridging when they have a low INR. There is a need for research to inform an optimal approach to bridging LVAD patients for subtherapeutic INR in the outpatient setting by evaluating the risk of adverse events associated with LMWH vs UFH bridging.

The first chapter of this dissertation analyzed data from a retrospective cohort study to compare 30-day rates of bleeding and thrombotic events between patients bridged with LMWH vs UFH for unexpected subtherapeutic INR occurring in the ambulatory setting. This study is novel in that it focused on LVAD patients who have been stable on warfarin anticoagulation but develop an unexpectedly low INR result, rather than on situations where the INR is low because warfarin was intentionally held (e.g., for a procedure). Given the lack of a clinical guideline on how to manage subtherapeutic INR in the chronic therapy phase following hospital discharge, it is important to understand the outcomes of bridging options in this setting.

The second chapter used parameters from the retrospective cohort study as model inputs into a decision analytic model to assess the cost-effectiveness of implementing outpatient LMWH bridging, as compared to intravenous UFH therapy, from the healthcare perspective. Elucidating the costs and health implications of alternative anticoagulation management strategies is important to optimize the care of patients after LVAD implantation under healthcare resource constraints. We also used probabilistic Monte Carlo simulation to characterize uncertainty surrounding the results of the cost-effectiveness analysis of LMWH vs UFH bridging.

In the third chapter, we performed value of information (VOI) analyses to quantify the potential value of a trial assessing the relative safety and efficacy of these bridging strategies and

to determine the optimal sample size of such a trial. VOI methods [13-16] provide an approach for weighing the benefits of reducing the uncertainty around the relative efficacy and safety of LMWH vs UFH bridging against the expected costs. As there is potential bias in the adverse event rates associated with LMWH/UFH bridging due to the retrospective study design in Aim 1, we ask and answer the question, "How much bias would there have to be (from Aim 1) in order to have some value of information from a future study?" We vary the "priors" for the event rates found from Aim 1 to account for potential bias and see what types of bias might lead to a non-zero or substantial value of information.

Overall, this dissertation contributes to informing decision making around the long-term anticoagulation management of patients after hospital discharge following LVAD implantation to prevent life-threatening thromboembolic complications. It also considers existing knowledge and uncertainty to determine the value of new research, which is an important step in setting an appropriate research agenda.

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Chapter 2 Comparative Effectiveness of Low Molecular Weight Heparin vs Unfractionated Heparin Therapy in Patients With Left Ventricular Assist Devices

Abstract

Patients with left ventricular assist devices (LVAD) use warfarin to prevent life-threatening thromboembolic complications. Warfarin requires temporary "bridging" anticoagulation when subtherapeutic. Comparative effectiveness data between hospitalization for unfractionated heparin (UFH) and outpatient management with low-molecular-weight heparin (LMWH) are lacking. We conducted a retrospective cohort study of adults with LVAD implantation between January 1, 2014 and December 31, 2018 from two academic medical centers. Data were collected for each unintended outpatient subtherapeutic INR episode for which either bridging UFH or LMWH was used. Records were reviewed for 30 days after bridging UFH or LMWH was discontinued, assessing for bleeding and/or thromboembolic events. Multivariable logistic regression analysis adjusted for site- and patient-level clustering along with LVAD type, HAS-BLED score for bleed risk, BMI and aspirin dosage. The composite outcome was major bleeding or thromboembolism.

Data were collected from 269 patients and 1364 bridging episodes. An aspirin dosage of >100 mg daily (OR: 4.99; 95% CI: 3.16-7.88; p<0.001) was a strong predictor of LMWH use. Compared to HeartMate 3, having a HeartMate II LVAD (OR: 0.30; 95% CI: 0.13-0.70; p=0.005) or Heartware HVAD (OR: 0.25; 95% CI: 0.14-0.44; p<0.001) was associated with lower odds of LMWH use. The 30-day rates of major bleeding or thromboembolism was

significantly lower for patients receiving LMWH as compared to UFH (11/1169 [0.9%] vs. 8/195 [4.1%]; $p<0.001$) in bivariate analyses. After adjusting for covariates and for site- and patient-level clustering, LMWH bridging was associated with a non-statistically significantly reduced risk of major adverse events for LVAD patients with subtherapeutic INR, compared to UFH therapy (OR: 0.44; 95% CI: 0.13-1.45; $p=0.177$). Larger, prospective studies are warranted to see if non-significant lower adverse event rates with inpatient UFH bridging therapy warrant increased healthcare resource utilization as compared to outpatient LMWH.

2.1 Introduction

Left ventricular assist devices (LVADs) are surgically implanted devices that support the circulation system in patients with advanced heart failure, either as bridge to cardiac transplant or as destination therapy for patients ineligible for transplant [1,2]. Without appropriate anticoagulation therapy, patients with LVADs are at risk for life-threatening thrombotic complications, such as pump thrombosis and systemic embolism [3]. To prevent thrombosis, all patients with LVADs are anticoagulated with warfarin, usually with a target international normalized ratio (INR) range of 2.0 - 3.0 [4,5]. LVAD patients often spend more than half of their time with low INR values (INR < 2.0), placing them at risk for thromboembolic complications [6-8].

The 2013 International Society for Heart and Lung Transplantation Guidelines support the use of unfractionated heparin (UFH) bridging for subtherapeutic INR levels in the immediate post-implantation period until anticoagulation with warfarin can be optimized [4]. However, there is no guidance on how to manage subtherapeutic INR values after the immediate post-implantation period. Given a lack of clinical trial data, bridging practice for low INR values varies widely between different LVAD centers. Outpatient treatment with LMWH is more convenient and less costly than a hospital admission for intravenous UFH therapy. However, while some LVAD centers routinely use outpatient LMWH bridging, some LVAD centers hospitalize their patients for UFH bridging when they have a low INR.

To date, there have not been studies evaluating the risk of adverse events associated with LMWH vs UFH bridging for subtherapeutic INR in the outpatient setting. Therefore, the aim of this study was to compare rates of bleeding and thrombotic events at 30-day between patients

bridged with LMWH vs UFH for unexpected subtherapeutic INR occurring in the outpatient setting.

2.2 Methods

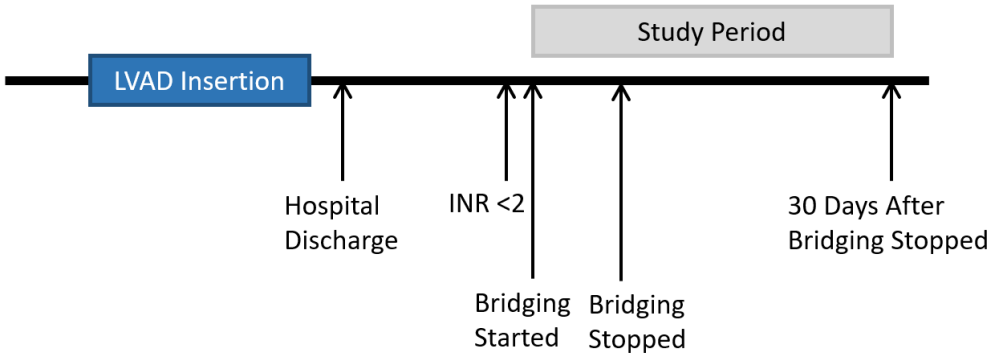
2.2.1 Study Population

We conducted a retrospective cohort study of patients aged 18 years and older with LVAD implantation between January 1, 2014 and December 31, 2018 at the University of Michigan Medical Center and at the Medical College of Wisconsin. Patients with total artificial heart or biventricular assist device were excluded.

2.2.2 Data Collection

Data were collected via retrospective chart audits for each episode of an unintentional INR value < 2 (after initial hospital discharge following LVAD implantation) occurring in the ambulatory setting where either UFH or LMWH bridging was administered. Chart abstractors excluded cases where the low INR values was associated with a planned surgical procedure. The patients' electronic medical records were reviewed for 30 days following discontinuation of bridging UFH or LMWH and any bleeding or thrombotic complications were recorded (Figure 1). Episodes of recurrent bridging before an adverse event in the 30-day period were excluded. This project was reviewed and approved with a waiver of informed consent by the Institutional Review Boards of both participating centers.

Figure 2.1 Study Design



2.2.3 Study Outcomes

The primary outcome was the composite outcome of major bleeding or thromboembolism occurring between 1 day after the start of bridging and 30 days after bridging was discontinued. Major bleeding and thromboembolism events were also evaluated separately as secondary outcomes.

Per the International Society on Thrombosis and Haemostasis, major bleeding was defined as fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome and/or bleeding causing a fall in hemoglobin level of 2 g dL or more, or leading to transfusion of two or more units of red blood cells [9]. Thromboembolism included ischemic stroke, systemic embolism, and pump thrombosis as identified through chart audit.

2.2.4 Statistical Analysis

Descriptive statistics were used for demographic and clinical characteristics at both the patient level and bridging episode level. Continuous variables are described with median (interquartile range [IQR]) and categorical variables are described in percentages. We calculated the HAS-BLED score, which is a validated and frequently used tool to estimate the risk of major bleeding in patients receiving anticoagulation for atrial fibrillation [10], based on the presence of the following risk factors: hypertension, renal disease, liver disease, stroke history, prior major bleeding or predisposition to bleeding, age >65, medication usage predisposing to bleeding, and alcohol use. Labile INR was not included in the calculation of HAS-BLED score, given that all patients were bridged for subtherapeutic INR. We examined differences in demographic and clinical characteristics across bridging type. Chi-squared tests were used to assess the associations between categorical variables and bridging type, and t-tests were used to test for a difference in means in continuous variables between LMWH vs. UFH bridging.

We also examined trends in the numbers of LMWH vs UFH bridging episodes by quarter-year. The remaining analyses were performed at the bridging episode level. To identify demographic and clinical predictors of LMWH use, multilevel logistic regression was used, adjusting for LVAD type and aspirin dosage, as these characteristics were significantly associated with LMWH use in univariable analyses. We also accounted for clustering at the patient level by including patient ID as a random effect.

Bivariate analyses were performed to assess associations between bridging type and the composite outcome of major bleeding or thromboembolism (as well as major bleeding and thromboembolism separately) within 30 days after LMWH or UFH was discontinued. Adverse

event rates and frequencies by bridging type were also assessed among low bleed risk (defined as having a HAS-BLED score of 1-2) and high bleed risk (defined as having a HAS-BLED score of ≥3) patients.

A multilevel logistic regression analysis was conducted to compare the odds of 30-day major bleeding or thromboembolism between LMWH and UFH bridging, adjusting for HAS-BLED score *a priori*. We also accounted for clustering at both the site and patient levels by including study site as a fixed effect and patient ID as a random effect. In bivariate analyses, LVAD type, BMI, and aspirin dosage were significantly associated with bridging type, so these patient characteristics were also included as covariates in the multilevel logistic regression model. Though HAS-BLED score was not associated with bridging type, HAS-BLED score was also adjusted for *a priori*, as it is a measure of disease severity and comorbidity and could affect selection into treatment (i.e., bridging type). Additionally, we ran the multilevel logistic regression model in the subset of high bleed risk patients (defined as having a HAS-BLED score of ≥3).

As a robustness check, we tested for autocorrelation. It is possible that the effect of LMWH treatment on major bleeding or thromboembolism changes with an increase in bridging episodes. We accounted for this by controlling for the number of episodes. A p-value ≤0.05 was considered statistically significant. All statistical analyses were performed using Stata version 17.0 (StataCorp; College Station; TX).

2.3 Results

2.3.1 Baseline Characteristics

A total of 269 patients and 1,364 bridging episodes were included in the analysis. Appendix Table 1 shows patient-level characteristics. They are stratified by whether the patient received LMWH, UFH or both in Appendix Table 2. Appendix Table 3 shows bridging episode-level baseline characteristics, and differences in patient characteristics across bridging type are shown in Appendix Table 4. The patients underwent LVAD implantation with HeartMate 3 (n = 63), HeartMate II (n = 29), and Heartware HVAD (n = 176). The majority (85.7%) of bridging episodes were LMWH. The distribution of low INR values between 1 and 1.9 (n=1,364) is shown in Appendix Figure 1, and the mean INR (and standard deviation) over the study period is shown in Appendix Figure 2. In 80.2% of episodes, additional courses of bridging were administered within 30 days, of which 86.3% were with LMWH. The number and percent of episodes that were LMWH vs UFH by quarter-year are shown in Appendix Figure 3.

2.3.2 Predictors of Bridging Type

Adjusting for clustering at the patient level, an aspirin dosage of >100 mg daily was associated with a higher odds of LMWH use (adjusted OR [aOR]: 4.99; 95% CI: 3.16-7.88, $p<0.001$), compared to an aspirin dosage of ≤100 mg daily. Compared to HeartMate 3, having a HeartMate II LVAD (aOR: 0.30, 95% CI: 0.13-0.70, $p=0.005$) or Heartware HVAD (aOR: 0.25; 95% CI: 0.14-0.44, $p<0.001$) was associated with lower odds of LMWH use (Appendix Table 5).

2.3.3 Outcomes

There were a total of 11/1169 (0.9%) major bleeding or thromboembolism events in the LMWH group vs 8/195 (4.1%) in the UFH group (p<0.001). With regards to major bleeding events only, there were 9/1169 (0.8%) events in the LMWH group as compared to 8/195 (4.1%) events in the UFH group (p<0.001). There were 2/1169 (0.2%) thromboembolism events in the LMWH group vs 0/195 (0%) in the UFH group (p=0.56) (Table 2.1). Adverse event rates and frequencies by bridging type among low and high bleed risk patients are shown in Appendix Tables 6 and 7.

After adjusting for LVAD type, HAS-BLED score, BMI, aspirin dosage, and clustering at the site and patient levels, LMWH use was associated with a non-statistically significantly reduced risk of 30-day major bleeding or thromboembolism as compared to UFH use (OR: 0.44, 95% CI: 0.13-1.45, p=0.18) (Table 2.2). However, in the subset of high bleed risk patients, LMWH use was associated with significantly reduced risk of 30-day major bleeding or thromboembolism as compared to UFH use (OR: 0.23, 95% CI: 0.06-0.81, p=0.023) (Appendix Table 8). Our test of autocorrelation revealed that the effect of LMWH treatment on major bleeding or thromboembolism does not meaningfully change with an increase in bridging episodes (OR: 0.46, 95% CI: 0.13-1.59) (Appendix Table 9).

Table 2.31 30-day adverse clinical event rates and frequencies

Variable	LMWH (N = 1,169)	UFH (N = 195)	Total (N = 1,364)	P-value
Major Bleeding or Thromboembolism, N (%)				
No	1,158 (99.1)	187 (95.9)	1,345 (98.6)	<0.001
Yes	11 (0.9)	8 (4.1)	19 (1.4)	
Major Bleeding, N (%)				
No	1,160 (99.2)	187 (95.9)	1,347 (98.8)	<0.001
Yes	9 (0.8)	8 (4.1)	17 (1.3)	
Thromboembolism, N (%)				
No	1,167 (99.8)	195 (100.0)	1,362 (99.9)	0.563
Yes	2 (0.2)	0 (0.0)	2 (0.2)	

Table 2.32 Results of two-level multivariable logistic regression analysis examining the association between LMWH use and 30-day major bleeding or thromboembolism

Characteristics	**Major Bleeding or Thromboembolism**	
	Adjusted Odds Ratio (aOR) 95% Confidence Interval (CI)*	**P-value**
LMWH Use	0.44 (0.13-1.45)	0.177
Type of LVAD		
Heartmate 3	1 [Referent]	
Heartmate II	2.19 (0.28-17.33)	0.457
Heartware HVAD	2.11 (0.41-10.82)	0.371
HAS-BLED Score	1.66 (0.82-3.36)	0.156
BMI	1.06 (0.99-1.14)	0.116
Aspirin Dosage		
≤100 mg daily	1 [Referent]	
>100 mg daily	1.41 (0.32-6.29)	0.652

*Accounted for clustering at both the site and patient levels by including study site as a fixed effect and patient ID as a random effect

2.4 Discussion

Among 269 patients and 1364 episodes of subtherapeutic INR, the combined risk of major bleeding or thromboembolism was non-statistically significantly reduced for LMWH versus UFH bridging anticoagulation use. We also found that LVAD type and aspirin use of >100 mg daily are predictors of LMWH use.

Another interesting finding from our study is that the percentage of bridging episodes with LMWH appears to have declined from 100% in the first quarter of 2014 to about 70% by mid-2018 and has increased since then to 96% by the end of the study period. This reflects a change in practice at the Medical College of Wisconsin due to new leadership who thought UFH is the optimal bridging anticoagulation strategy and highlights the importance of the project to understand the outcomes of bridging options.

Given a lack of clinical trial data, bridging practice for low INR varies widely between different LVAD centers. While some LVAD centers routinely use outpatient LMWH bridging, other LVAD centers hospitalize their patients for continuous UFH bridging [11]. Our study did not find a statistically significant differences in adverse event rates between the LMWH and UFH groups. This finding was robust to a test for autocorrelation. Notably, after adjusting for covariates and clustering at the patient- and center-level, the odds ratio point estimate for adverse events was 0.44. This means that a larger study may have identified a significantly reduced risk of adverse events when LMWH is used for subtherapeutic INR bridging as compared to UFH. If this were to be confirmed in larger studies, it would have significant impact for healthcare resource utilization, as UFH requires hospital admission. However, if LMWH is confirmed to have no significant increased risk of adverse events, then hospitalization can be avoided and resource utilization reduced with LMWH bridging. In the subset of high bleed risk patients, LMWH was associated with a significantly reduced risk of major adverse events, highlighting that the effect of LMWH treatment may vary by risk status. Further investigation of heterogeneity of treatment effects over patient subgroups would also benefit from a larger sample size.

This study is novel in that it compares adverse event rates in LVAD patients bridged with either UFH or LMWH in the outpatient setting. A previous study focusing on the immediate and early postoperative period after LVAD implantation found no significant difference in cerebral vascular accidents or bleeding events between LMWH and UFH [12]. Other studies reported the number of adverse events associated with LMWH but did not look at a comparator intervention [13-16]. One study comparing LMWH to no bridging anticoagulation in the outpatient setting found similar major bleeding event rates [17]. Finally, studies have compared LMWH to UFH

bridging in other clinical situations requiring anticoagulation (e.g., atrial fibrillation) [18-21]. In general, these studies have not found meaningful differences in clinical outcomes between various methods for bridging anticoagulation.

There are some important limitations of our study. First, our study is a retrospective analysis of patients cared for in only two medical centers. Both medical centers are in the Midwest, thereby limiting generalizability to other parts of the nation. In addition, while we controlled for potential confounders and for clustering at the site and patient levels in our analysis, unobserved confounding can still bias estimate of the effect of bridging type on bleeding and thrombotic outcomes in any retrospective, observational analysis. This includes unmeasured reasons why a clinician may have selected UFH as the preferred bridging agent for a specific patient and situation. Finally, the relatively small sample size in our study warrants a larger prospective evaluation to confirm our findings.

2.5 Conclusion

In this two-center, retrospective study of 269 patients with LVAD, outpatient LMWH bridging was associated with a non-statistically significantly lower risk of major adverse events as compared to inpatient UFH bridging for unintended, subtherapeutic INRs in the ambulatory setting. A well powered, prospective comparison of these two anticoagulation management strategies in LVAD patients is warranted.

2.6 References

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2.7 Appendix

Figure 2.A.1 Distribution of Low INR Values for All-Risk Patients

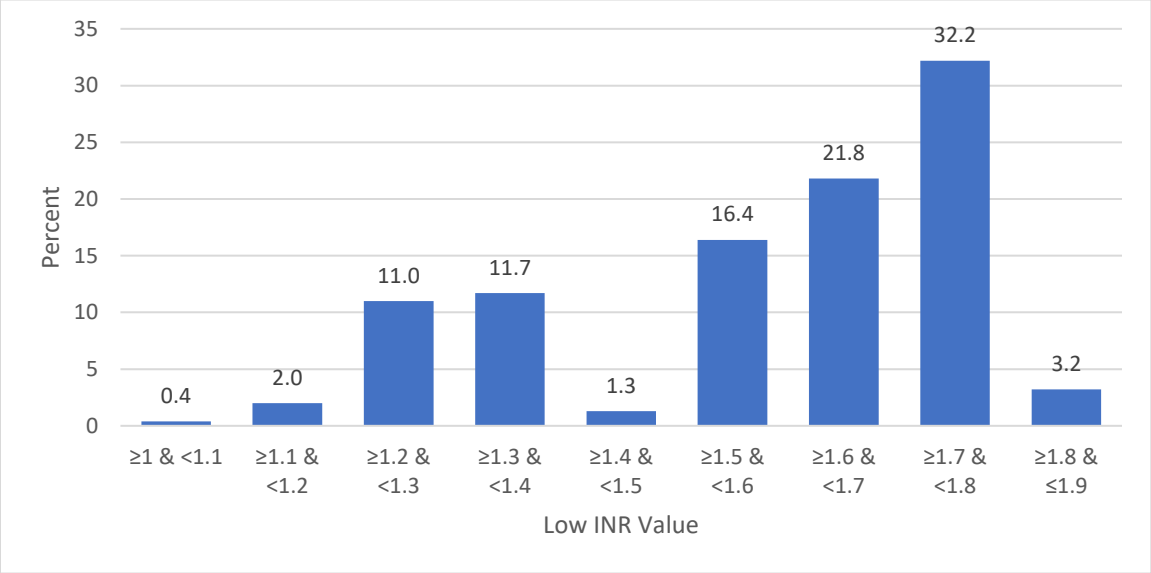


Figure 2.A.2 Mean INR Over Study Period for All-Risk Patients

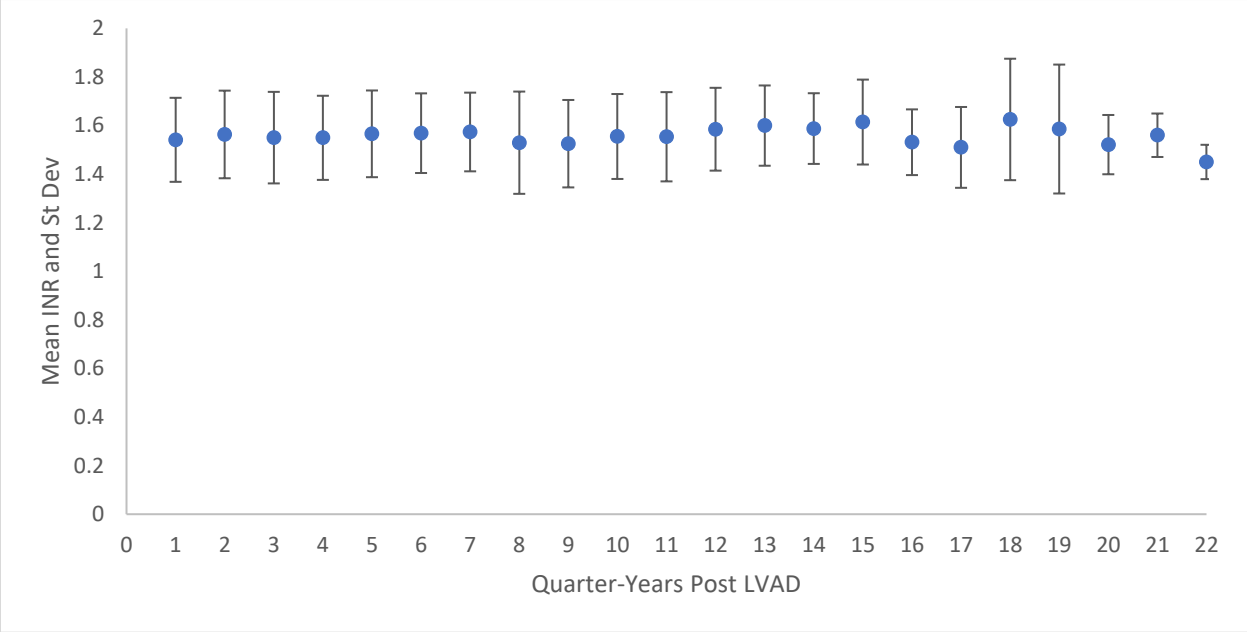


Figure 2.A.3 UFH vs. LMWH Bridging Episodes by Quarter

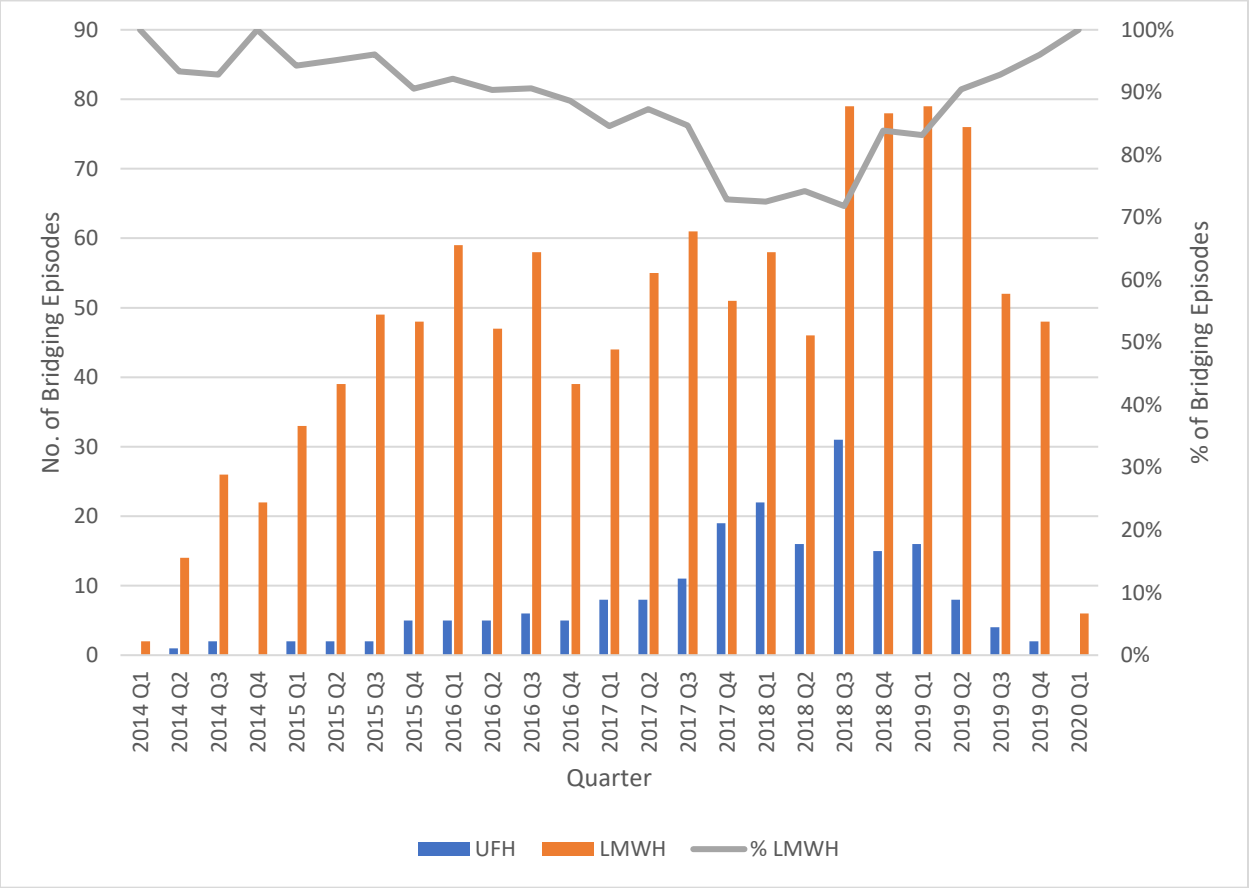


Table 2.A.1 Patient-Level Characteristics

Characteristic	**Total (n=269)**
	N (%)
Study Site	
University of Michigan	202 (75.1)
Medical College of Wisconsin	67 (24.9)
Bridging Type	
Patients bridged UFH only	22 (8.2)
Patients bridged with LMWH only	156 (58.0)
Patients bridged with Both	91 (33.8)
Percent of bridging episodes that were LMWH among patients who were bridged with both	78.7%
Age at time of LVAD implantation	
Mean (SD)	53.5 (14.1)
18-34	34 (12.6)
35-49	49 (18.2)
50-64	125 (46.5)
65-84	61 (22.7)
Sex	
Male	204 (75.8)
Female	65 (24.2)
Type of LVAD	
HeartMate 3	63 (23.5)
HeartMate II	29 (10.8)
Heartware HVAD	176 (65.7)
Discharge Location after LVAD implantation	
Home	246 (91.5)
Rehab	17 (6.3)
Other	6 (2.2)
HAS-BLED Score	
1	40 (14.9)
2	74 (27.6)
3	143 (53.4)
4	9 (3.4)
5	2 (0.8)

BMI	
Mean (SD)	27.7 (6.3)
Underweight (< 18.5)	13 (4.8)
Normal (≥ 18.5 & < 25.0)	86 (32.0)
Overweight (≥ 25.0 & < 30.0)	80 (29.7)
Obese (≥ 30.0)	90 (33.5)
Initial INR Target Range	
2-3	264 (98.1)
Other	5 (1.9)
Duration of follow-up per patient (from each individual's LVAD implantation to last bridging episode) (in days)	
Mean (SD)	531.4 (456.1)
28-154	65 (24.2)
155-429	71 (26.4)
430-729	62 (23.1)
730-1959	71 (26.4)
Number of bridging episodes	
Mean (SD)	5.3 (4.8)
1-2	86 (32.0)
3-4	65 (24.2)
5-7	57 (21.2)
8-34	61 (22.7)

Table 2.A.2 Patient-Level Characteristics by Bridging Type

Characteristic	**Outpatient LMWH only (n=156)**	**Inpatient UFH only (n=22)**	**Both (n=91)**
	N (%)	**N (%)**	**N (%)**
Study Site			
University of Michigan	138 (88.5)	2 (9.1)	62 (68.1)
Medical College of Wisconsin	18 (11.5)	20 (90.9)	29 (31.9)
Age at time of LVAD implantation			
Mean (SD)	53.0 (14.4)	57.3 (12.7)	53.3 (13.9)
18-34	21 (13.5)	2 (9.1)	11 (12.1)
35-49	29 (18.6)	0 (0.0)	20 (22.0)
50-64	69 (44.2)	14 (63.6)	42 (46.2)
65-84	37 (23.7)	6 (27.3)	18 (19.8)
Sex			
Male	117 (75.0)	16 (72.7)	71 (78.0)
Female	39 (25.0)	6 (27.3)	20 (22.0)
Type of LVAD			
HeartMate 3	44 (28.4)	3 (13.6)	16 (17.6)
HeartMate II	16 (10.3)	2 (9.1)	11 (12.1)
Heartware HVAD	95 (61.3)	17 (77.3)	64 (70.3)
Discharge Location after LVAD implantation			
Home	145 (93.0)	17 (77.3)	84 (92.3)
Rehab	6 (3.9)	5 (22.7)	6 (6.6)
Other	5 (3.2)	0 (0.0)	1 (1.1)
HAS-BLED Score			
1	18 (11.5)	5 (22.7)	17 (18.9)
2	44 (28.2)	8 (36.4)	23 (25.6)
3	87 (55.8)	9 (40.9)	46 (51.1)
4	6 (3.9)	0 (0.0)	3 (3.3)
5	1 (0.6)	0 (0.0)	1 (1.1)
BMI			
Mean (SD)	27.3 (6.1)	28.0 (7.7)	28.4 (6.3)
Underweight (< 18.5)	8 (5.1)	1 (4.6)	4 (4.4)
Normal (≥ 18.5 & < 25.0)	54 (34.6)	8 (36.4)	24 (26.4)

Overweight (≥ 25.0 & < 30.0)	43 (27.6)	5 (22.7)	32 (35.2)
Obese (≥ 30.0)	51 (32.7)	8 (36.4)	31 (34.1)
Initial INR Target Range			
2-3	153 (98.1)	21 (95.5)	90 (98.9)
Other	3 (1.9)	1 (4.6)	1 (1.1)
Duration of follow-up per patient (from each individual's LVAD implantation to last bridging episode) (in days)			
Mean (SD)	480.9 (425.5)	131.3 (132.0)	714.8 (475.3)
28-154	42 (26.9)	16 (72.7)	7 (7.7)
155-429	42 (26.9)	5 (22.7)	24 (26.4)
430-729	40 (25.6)	1 (4.6)	21 (23.1)
730-1959	32 (20.5)	0 (0.0)	39 (42.9)
Number of bridging episodes			
Mean (SD)	4.0 (3.3)	2.0 (1.4)	8.4 (5.9)
1-2	65 (41.7)	14 (63.6)	7 (7.7)
3-4	38 (24.4)	6 (27.3)	21 (23.1)
5-7	33 (21.2)	2 (9.1)	22 (24.2)
8-34	20 (12.8)	0 (0.0)	41 (45.1)

Table 2.A.3 Bridging Episode-Level Characteristics (n=1,364)

Characteristic	**N (%)**
Bridging Type	
UFH	195 (14.3)
LMWH	1,169 (85.7)
Low INR Value	
Mean (SD)	1.6 (0.2)
≥1 & <1.5	359 (26.5)
≥1.5 & <1.7	517 (38.1)
≥1.7 & ≤1.9	480 (35.4)
Duration of bridging (in days)	
Mean (SD)	6.8 (7.0)
0-2	266 (19.5)
3-5	497 (36.5)
6-9	327 (24.0)
10-83	273 (20.0)
Additional course of bridging administered in 30-day period	
No	270 (19.8)
Yes	1,094 (80.2)
UFH	150 (13.7)
LMWH	944 (86.3)
Hospitalization for bridging	
No	1,161 (85.4)
Yes	199 (14.6)
UFH	195 (98.0)
LMWH	4 (2.0)
Duration of hospitalization for bridging, if hospitalized (in days)	
Mean (SD)	5.8 (4.8)
0-2	38 (26.6)
3-5	54 (37.8)
6-9	24 (16.8)
10-27	27 (18.9)
Antiplatelet medications at time of bridging	
ASA	633 (47.9)
P2Y12 inhibitor	3 (0.2)
Dipyridamole	686 (51.9)

Aspirin dosage	
≤100 mg daily	270 (19.8)
>100 mg daily	1,094 (80.2)

Table 2.A.4 Differences in Patient Characteristics Across Bridging Type

Characteristic	**Outpatient management with LMWH (n=1,169)**	**Inpatient UFH therapy (n=195)**	**P-value**
	N (%)	**N (%)**	
Age at time of LVAD implantation			
Mean (SD)	51.0 (14.2)	52.8 (13.3)	0.090
Sex			
Male	891 (76.2)	151 (77.4)	0.711
Female	278 (23.8)	44 (22.6)	
Type of LVAD			
HeartMate 3	304 (26.0)	32 (16.4)	0.013
HeartMate II	137 (11.7)	23 (11.8)	
Heartware HVAD	727 (62.2)	140 (71.8)	
HAS-BLED Score			
Mean (SD)	2.5 (0.8)	2.4 (0.9)	0.087
BMI			
Mean (SD)	27.8 (6.2)	28.9 (7.0)	0.038
Number of bridging episodes			
Mean (SD)	5.5 (4.9)	5.0 (5.0)	0.186
Low INR Value			
Mean (SD)	1.6 (0.2)	1.6 (0.2)	0.427
Additional course of bridging administered in 30-day period			
No	41 (3.5)	12 (6.2)	0.077
Yes	1,128 (96.5)	183 (93.9)	

Duration of hospitalization for bridging, if hospitalized (in days)			
Mean (SD)	2.5 (3.0)	5.9 (4.9)	0.103
Aspirin dosage			
≤100 mg daily	202 (17.6)	67 (39.2)	<0.001
>100 mg daily	943 (82.4)	104 (60.8)	

Table 2.A.5 Predictors of LMWH Use

Characteristics	**LMWH Use**			
	Odds Ratio (OR) 95% Confidence Interval (CI)	**P-value**	**Adjusted Odds Ratio (aOR) 95% Confidence Interval (CI)***	**P-value**
Type of LVAD				
Heartmate 3	1 [Reference]		1 [Reference]	
Heartmate II	0.42 (0.15-1.18)	0.099	0.30 (0.13-0.70)	0.005
Heartware HVAD	0.41 (0.21-0.83)	0.013	0.25 (0.14-0.44)	<0.001
Aspirin dosage				
≤100 mg daily	1 [Reference]		1 [Reference]	
>100 mg daily	3.48 (2.20-5.50)	<0.001	4.99 (3.16-7.88)	<0.001
Sex				
Male	1 [Reference]			
Female	1.18 (0.62-2.25)	0.618		
Additional course of bridging administered in 30-day period				
No	1 [Reference]			
Yes	1.04 (0.67-1.62)	0.863		

Abbreviations: CI, confidence interval; aOR, adjusted odds ratio
*Multivariable model built including all variables with a $p<0.05$ in univariable analyses.
Adjusted for clustering at the patient level.

Table 2.A.6 30-day adverse clinical event rates and frequencies among low bleed risk patients

Variable	LMWH (N = 472)	UFH (N = 85)	Total (N = 557)	p-value
Major Bleeding or Thromboembolism, N (%)				
No	468 (99.2)	82 (96.5)	550 (98.7)	0.041
Yes	4 (0.9)	3 (3.5)	7 (1.3)	
Major Bleeding, N (%)				
No	469 (99.4)	82 (96.5)	551 (98.9)	0.017
Yes	3 (0.6)	3 (3.5)	6 (1.1)	
Thromboembolism, N (%)				
No	471 (99.8)	85 (100.0)	556 (99.8)	0.671
Yes	1 (0.2)	0 (0.0)	1 (0.2)	

Low bleed risk defined as having a HAS-BLED score of 1-2.

Table 2.A.7 30-day adverse clinical event rates and frequencies among high bleed risk patients

Variable	LMWH (N = 697)	UFH (N = 107)	Total (N = 804)	p-value
Major Bleeding or Thromboembolism, N (%)				
No	690 (99.0)	102 (95.3)	792 (98.5)	0.004
Yes	7 (1.0)	5 (4.7)	12 (1.5)	
Major Bleeding, N (%)				
No	691 (99.1)	102 (95.3)	793 (98.6)	0.002
Yes	6 (0.9)	5 (4.7)	11 (1.4)	
Thromboembolism, N (%)				
No	696 (99.9)	107 (100.0)	803 (99.9)	0.695
Yes	1 (0.1)	0 (0.0)	1 (0.1)	

High bleed risk defined as having a HAS-BLED score of ≥3.

Table 2.A.8 Results of two-level multivariable logistic regression analysis examining the association between LMWH use and 30-day major bleeding or thromboembolism in the subgroup of high bleed risk patients

Characteristics	**Major Bleeding or Thromboembolism**	
	Adjusted Odds Ratio (aOR) 95% Confidence Interval (CI)*	**P-value**
LMWH Use	0.23 (0.06-0.81)	0.023
Type of LVAD		
Heartmate 3	1 [Referent]	
Heartmate II	1.63 (0.19-13.87)	0.653
Heartware HVAD	1.18 (0.20-7.10)	0.859
BMI	1.04 (0.94-1.16)	0.441
Aspirin Dosage		
≤100 mg daily	1 [Referent]	
>100 mg daily	1.70 (0.29-9.98)	0.555

*Accounted for clustering at both the site and patient levels by including study site as a fixed effect and patient ID as a random effect

High bleed risk defined as having a HAS-BLED score of ≥3.

Table 2.A.9 Results of two-level multivariable logistic regression analysis examining the association between LMWH use and 30-day major bleeding or thromboembolism, adjusting for number of episodes

Characteristics	**Major Bleeding or Thromboembolism**	
	Adjusted Odds Ratio (aOR) 95% Confidence Interval (CI)	**P-value**
LMWH use	0.46 (0.13-1.59)	0.221
Type of LVAD		
Heartmate 3	1 [Referent]	
Heartmate II	1.60 (0.12-22.01)	0.724
Heartware HVAD	2.30 (0.32-16.42)	0.405
HAS-BLED score	1.82 (0.56-5.95)	0.322
BMI	1.07 (0.97-1.18)	0.174
Aspirin dosage		
≤100 mg daily	1 [Referent]	
>100 mg daily	1.24 (0.22-7.03)	0.806
Number of bridging episodes	1.14 (0.76-1.69)	0.530

Chapter 3 Cost-Effectiveness Analysis of Low Molecular Weight Heparin vs Unfractionated Heparin Therapy in Patients With Left Ventricular Assist Devices

Abstract

Patients with left ventricular assist devices (LVAD) often require temporary "bridging" anticoagulation to prevent life-threatening thromboembolic complications. Given a lack of clinical trial data, bridging practice varies widely between different LVAD centers. This study evaluated the cost-effectiveness of outpatient management with low-molecular-weight heparin (LMWH) vs hospitalization with unfractionated heparin (UFH).

We projected health and economic outcomes for LMWH vs UFH bridging strategies using a decision analytic model parameterized using data on rates of bleeding and thrombotic events and deaths from a two-center retrospective cohort study of adults with LVAD implantation between January 2014 and December 2018 and from the published literature. Base case analyses used a healthcare sector perspective. The primary outcome was the incremental cost-effectiveness ratio in 2021 US dollars per quality-adjusted life year (QALY) gained. Sensitivity analyses were conducted.

The base-case cost-effectiveness analysis showed that outpatient management with LMWH was cost-saving. In probabilistic sensitivity analyses, LMWH remained cost-saving in 98.0% of iterations at a willingness to pay of $100,000/QALY. There appears to be little uncertainty that outpatient management with LMWH is more favorable than inpatient UFH bridging in LVAD patients.

3.1 Introduction

Left ventricular assist devices (LVADs) are used either as bridge to cardiac transplant or as destination therapy for patients ineligible for transplant [1,2]. Without appropriate anticoagulation therapy, patients with LVADs are at risk for life-threatening thrombotic complications, such as pump thrombosis and systemic embolism [3]. Patients with left ventricular assist devices (LVAD) use warfarin to prevent thrombosis. Warfarin's anticoagulant effects are notoriously variable, requiring the use of temporary "bridging" anticoagulation when subtherapeutic. While some LVAD centers routinely use outpatient low molecular weight heparin (LMWH) bridging, many LVAD centers hospitalize their patients for unfractionated heparin (UFH) bridging when they have a subtherapeutic international normalized ratio (INR).

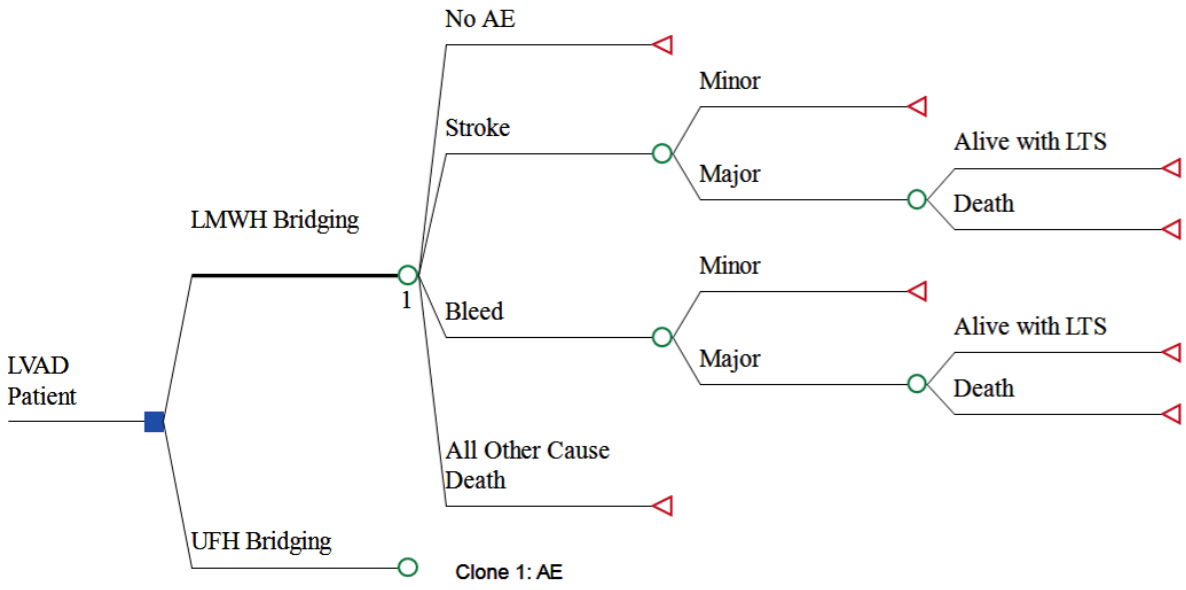
Our two-center retrospective cohort study found a reduced risk of adverse events when LMWH is used for subtherapeutic INR bridging as compared to UFH in the outpatient setting. As UFH requires hospital admission, there is higher healthcare resource utilization with UFH, compared to LMWH. To date, there have not been any economic evaluations of bridging LVAD patients with LMWH rather than UFH. In this study, we conducted a cost-effectiveness analysis to evaluate the potential cost savings of switching from inpatient UFH bridging to outpatient management with LMWH per patient by risk status. This would inform decisions by health care providers and payers to maximize health outcomes for patients following LVAD implantation on a limited budget. We also used probabilistic Monte Carlo simulation to characterize uncertainty surrounding the results of the cost-effectiveness analysis of LMWH vs UFH bridging anticoagulation.

3.2 Methods

3.2.1 Decision Model

A decision analysis model was developed to project the average costs and health gains per bridging episode for LVAD patients ages 18 years or older receiving LMWH vs. UFH but examining the effects of that bridging episode over a lifetime of the patient. Health gains were expressed in quality adjusted life-years (QALYs), as QALYs allow for comparison between health conditions due to the generic character of this outcome measure [2]. QALYs lost to an adverse event measure the overall reduction in a patient's well being, or health-related quality of life, due to the adverse event and its consequences (which may last a lifetime). A schematic of the decision tree is shown in Figure 3.1. The model predicted adverse events within 30 days after discontinuing bridging as adverse events would typically be attributable to bridging during this time interval. Adverse events included minor stroke, major stroke, death due to major stroke, minor bleed, major bleed, death due to major bleed, and death due to other causes. The final outcome as shown at the terminal nodes was survival (1 = alive with long-term sequelae, 0 = dead).

Figure 3.1 Decision tree model



Different costs and health utility weights were associated with the different 30-day bleeding and thrombotic outcomes following bridging. For both treatments, we projected the probabilities of adverse events, QALYs, and net costs over a lifetime. QALYs were calculated by multiplying length of time spent in each health state by the utility associated with the health state. Age-specific utility weights for the LVAD population were derived from baseline age-specific utility weights from the general population [4] and a utility decrement associated with having an LVAD [5]. Disease-specific utility weights were multiplied by age-specific utility weights for the LVAD population to estimate overall utility. For example, the utility weight for a minor bleed was multiplied by age-specific utility weights for the LVAD population to estimate overall utility for a minor bleed. Long-term minor stroke, major stroke, and major bleed costs were discounted over 7 years, as mean survival for LVAD patients has been estimated to be 7.1 years [6].

The health sector perspective was analyzed and included direct medical costs borne by the individual and third-party payers, including costs of INR monitoring, bridging anticoagulation and adverse events. The societal perspective was not analyzed, as LVAD patients are typically unable to work due to disability and therefore may not incur productivity losses due to undergoing bridging anticoagulation therapy. In addition, to the best of our knowledge, there is no literature on health utility values and productivity costs associated with being a caregiver of an LVAD patient. The main endpoint for this analysis was the incremental cost-effectiveness ratio (ICER) of using LMWH compared with UFH bridging anticoagulation therapy, or the difference in cost between the two possible bridging strategies divided by the difference in the QALYs.

Analyses were conducted by bleed risk status and overall. Patients were stratified by their HAS-BLED score into low bleed risk (1-2) and high bleed risk (≥3). HAS-BLED score was based on the presence of the following risk factors: hypertension, renal disease, liver disease, stroke history, prior major bleeding or predisposition to bleeding, age >65, medication usage predisposing to bleeding, and alcohol use.

3.2.2 Data Sources

Table 3.1 shows the list of parameter inputs used in the model. Parameter estimates of differential rates of bleeding and thrombotic events and deaths conditional on receiving LMWH vs UFH therapy for all-risk patients as well as both low- and high-risk groups were derived from analysis of the data from our retrospective cohort study. In the retrospective cohort study, 40% of patients were low risk and 60% of patients were high risk.

Costs and health utilities were derived from published studies. Research has shown that the avoidance of the need for intravenous treatment administration is associated with an

improvement in health-related quality of life [7]. As receiving intravenous therapy is more invasive and inconvenient for patients than receiving a needle injection, the receipt of UFH therapy was given a utility decrement [8].

All costs were inflated to 2021 US dollars using the GDP Deflator [9]. Based on recommendations of the US Panel on Cost Effectiveness in Health and Medicine, all future costs and benefits were discounted at a 3% annual rate [3].

It was assumed that all-risk LVAD patients have an LVAD specific mortality rate as well as an all-cause mortality rate derived from the life table from the Centers for Disease Control and Prevention (Appendix Tables 1-2). Based on the published literature, we applied a lower LVAD specific mortality rate for low-risk patients and a higher LVAD specific mortality rate for high-risk patients (Appendix Tables 3-4). We also assumed that event rates for other conditions not included in the model are similar across both bridging therapies.

Table 3.21 Key model input parameters

Model parameter	Base case	Low	High	Distribution	Data source
Probabilities – LMWH					
Probability of bleed					
All patients	0.015	0.008	0.104	Beta	Retrospective cohort data, [1]
Low bleed risk subgroup	0.011	0.001	0.104	Beta	Retrospective cohort data, [1]
High bleed risk subgroup	0.018	0.008	0.104	Beta	Retrospective cohort data, [1]
Probability of major bleed given bleed					
All patients	0.529	0.292	0.767	Beta	Retrospective cohort data, [1]
Low bleed risk subgroup	0.6	0.171	1	Beta	Retrospective cohort data, [1]
High bleed risk subgroup	0.5	0.217	0.783	Beta	Retrospective cohort data, [1]
Probability of death given major bleed					
All patients	0.118	0	0.328	Beta	Retrospective cohort data, [1]
Low bleed risk subgroup	0.667	0.133	1	Beta	Retrospective cohort data, [1]
High bleed risk subgroup	0.05	0	0.2	Beta	Retrospective cohort data, [1], Assumption
Probability of stroke					
All patients	0.002	0	0.015	Beta	Retrospective cohort data, [1]
Low bleed risk subgroup	0.002	0	0.015	Beta	Retrospective cohort data, [1]
High bleed risk subgroup	0.001	0	0.015	Beta	Retrospective cohort data, [1]
Probability of major stroke given stroke					
All patients	0.95	0.8	1	Beta	Retrospective cohort data, [1], Assumption
Low bleed risk subgroup	0.95	0.8	1	Beta	Retrospective cohort data, [1],

					Assumption
High bleed risk subgroup	0.95	0.8	1	Beta	Retrospective cohort data, [1], Assumption
Probability of death given major stroke					
All patients	0.5	0	1	Beta	Retrospective cohort data, [1]
Low bleed risk subgroup	0.05	0	0.2	Beta	Retrospective cohort data, [1], Assumption
High bleed risk subgroup	0.95	0.8	1	Beta	Retrospective cohort data, [1], Assumption
Probabilities – UFH					
Probability of bleed					
All patients	0.041	0.013	0.149	Beta	Retrospective cohort data, [1]
Low bleed risk subgroup	0.036	0	0.149	Beta	Retrospective cohort data, [1]
High bleed risk subgroup	0.047	0.007	0.149	Beta	Retrospective cohort data, [1]
Probability of major bleed given bleed					
All patients	0.95	0.8	1	Beta	Retrospective cohort data, [1], Assumption
Low bleed risk subgroup	0.95	0.8	1	Beta	Retrospective cohort data, [1], Assumption
High bleed risk subgroup	0.95	0.8	1	Beta	Retrospective cohort data, [1], Assumption
Probability of death given major bleed					
All patients	0.25	0	0.55	Beta	Retrospective cohort data, [1]
Low bleed risk Subgroup	0.05	0	0.2	Beta	Retrospective cohort data, [1], Assumption
High bleed risk Subgroup	0.4	0	0.829	Beta	Retrospective cohort data, [1]
Probability of stroke					

All patients	0.01	0	0.019	Beta	Retrospective cohort data, [1]
Low bleed risk Subgroup	0.01	0	0.019	Beta	Retrospective cohort data, [1]
High bleed risk Subgroup	0.01	0	0.019	Beta	Retrospective cohort data, [1]
Probability of major stroke given stroke					
All patients	0.05	0	0.2	Beta	Retrospective cohort data, [1], Assumption
Low bleed risk Subgroup	0.05	0	0.2	Beta	Retrospective cohort data, [1], Assumption
High bleed risk subgroup	0.05	0	0.2	Beta	Retrospective cohort data, [1] Assumption
Probability of death given major stroke					
All patients	0.05	0	0.2	Beta	Retrospective cohort data, [1], Assumption
Low bleed risk subgroup	0.05	0	0.2	Beta	Retrospective cohort data, [1], Assumption
High bleed risk subgroup	0.05	0	0.2	Beta	Retrospective cohort data, [1], Assumption
Other Probabilities					
Probability of all other cause death					
All patients	0.168	0.16	0.18	Beta	[10],
Low bleed risk subgroup	0.14	0.13	0.15	Beta	[10], Assumption
High bleed risk subgroup	0.2	0.19	0.21	Beta	[10], Assumption
LVAD-specific mortality rate					
All patients	0.254	0.1	0.4	Beta	[16]
Low bleed risk subgroup	0.2	0.1	0.3	Beta	[16,17]
High bleed risk subgroup	0.3	0.2	0.4	Beta	[16,17]
Costs (in 2021 US $)					

Cost of intravenous UFH therapy	5,108	4,707	5,544	Nml	[11]
Cost of LMWH bridging	273	268	278	Nml	[12]
Warfarin and international normalized ratio monitoring, monthly	75.95	6.19	145.70	Nml, trunc	[13]
Event cost of minor bleeding	48.71	0	237.90	Nml, trunc	[13]
Event cost of major bleeding	48,651.00	34,870.00	62,435.00	Nml	[13]
Annual cost of major bleeding	40,783.80	2,134.31	79,419.72	Nml	[13]
Event cost of minor stroke	21,532.73	19,135.55	23,931.05	Nml	[13]
Annual cost of minor stroke	11,052.41	2,882.10	19,222.84	Nml	[13]
Event cost of major stroke	34,038.64	30,248.02	37,829.27	Nml	[13]
Annual cost of major stroke	17,469.02	4,540.54	30,383.94	Nml	[13]
Discount rate	0.03	0.01	0.05	Nml, trunc	[3]
Health-utility weights					
HRQL in LVAD patients	0.8	0.7	0.9	Beta	[14]
Disutility of major bleed, long-term	-0.40	-0.20	-0.60	Beta	[13]
Disutility of minor bleed	-0.13	-0.08	-0.13	Beta	[13]
Disutility of major stroke, first year	-0.74	-0.5	-0.8	Beta	[13]
Disutility of major stroke, long-term	-0.29	-0.04	-0.6	Beta	[13]
Disutility of minor stroke	-0.25	-0.15	-0.25	Beta	[13]
Disutility of intravenous therapy	-0.04	-0.02	-0.1	Beta	[7,8]

3.2.3 Sensitivity Analyses

We conducted one-way sensitivity analyses of all model inputs, varying each parameter within the defined value ranges. The binomial distribution was used to determine the lower bounds for probabilities of adverse events, and the upper bounds were informed by a study by Shah et al. (2020) focusing on index hospitalization and follow-up 3 months period after LVAD implantation that found that patients receiving LMWH have a non-significantly elevated risk of bleeding events as compared to UFH bridging for subtherapeutic INR (adjusted OR: 1.2, 95% CI = 0.54-2.84, p=0.62) [1].

We then conducted probabilistic sensitivity analysis (PSA) by assigning each uncertain input parameter in the analysis a plausible distribution and sampling each input parameter from their assigned distributions simultaneously using a Monte Carlo simulation. Distributions for parameter inputs are described in Table 3.1. The incremental result of each simulation iteration in the PSA was plotted and interpreted together with relevant Willingness-to-Pay (WTP) thresholds to provide an estimate of the probability of being cost-effective and the associated uncertainty around the incremental cost and effect results. The PSA results for different thresholds were represented by Cost-effectiveness Acceptability Curves (CEACs) [3].

Model creation and analyses were performed by using TreeAge Pro Suite 2020 R2.0 (TreeAge Software, Williamstown, Massachusetts) and Microsoft Excel 2019 (Microsoft, Redmond, Washington). The impact inventory is included in the Appendix Table 5.

3.3 Results

Table 3.31 Expected Values of Cost-effectiveness of LMWH vs UFH Bridging per LVAD Patient in the Base Case, By Bleed Risk and Overall

	Costs, $	**QALYs**	**Incremental costs, $**	**Incremental QALYs**	**ICER ($/QALY)**
All-risk patients					
UFH	11,445	1.70			
LMWH	1,765	1.77	-9,680	0.08	Cost-saving
Low bleed risk group					
UFH	12,288	2.16			
LMWH	1,181	2.22	-11,107	0.07	Cost-saving
High bleed risk group					
UFH	11,018	1.36			
LMWH	1,819	1.44	-9,199	0.08	Cost-saving

Table 3.2 shows the base-case cost-effectiveness results of LMWH vs. UFH bridging. Outpatient administration with LMWH was cost-saving compared to inpatient UFH therapy for all-risk patients as well as both low and high bleed risk groups. For all-risk patients, the total costs were $11,445 for UFH and $1,765 for LMWH. The total QALYs gained were 1.70 for UFH and 1.77 for LMWH. For the low bleed risk group, the total costs were $12,288 for UFH and $1,181 for LMWH. The total QALYs gained were 2.16 for UFH and 2.22 for LMWH. For the high bleed risk group, the total costs were $11,018 for UFH and $1,819 for LMWH. The total QALYs gained were 1.36 for UFH and 1.44 for LMWH. The projected probabilities of adverse events and disaggregated INR monitoring, bridging therapy, and adverse event costs per bridging episode are shown in Appendix Tables 6 and 7, respectively.

One-way sensitivity analyses of all parameters used in the decision tree model were conducted. We created a tornado diagram showing the ten most influential parameters for all-risk patients as well as both risk groups in terms of net monetary benefit, as LMWH was dominant. Net monetary benefit was calculated by multiplying QALYs by WTP and subtracting costs, assuming WTP for health as $100,000 per QALY. For all-risk patients and both risk groups, the cost-effectiveness of LMWH vs. UFH bridging was most sensitive to LVAD-specific mortality rate, followed by HRQL in LVAD patients and probability of bleed associated with LMWH bridging (Figures 3.2-3.4).

Figure 3.2 Tornado diagram of one-way sensitivity analysis results, all-risk patients

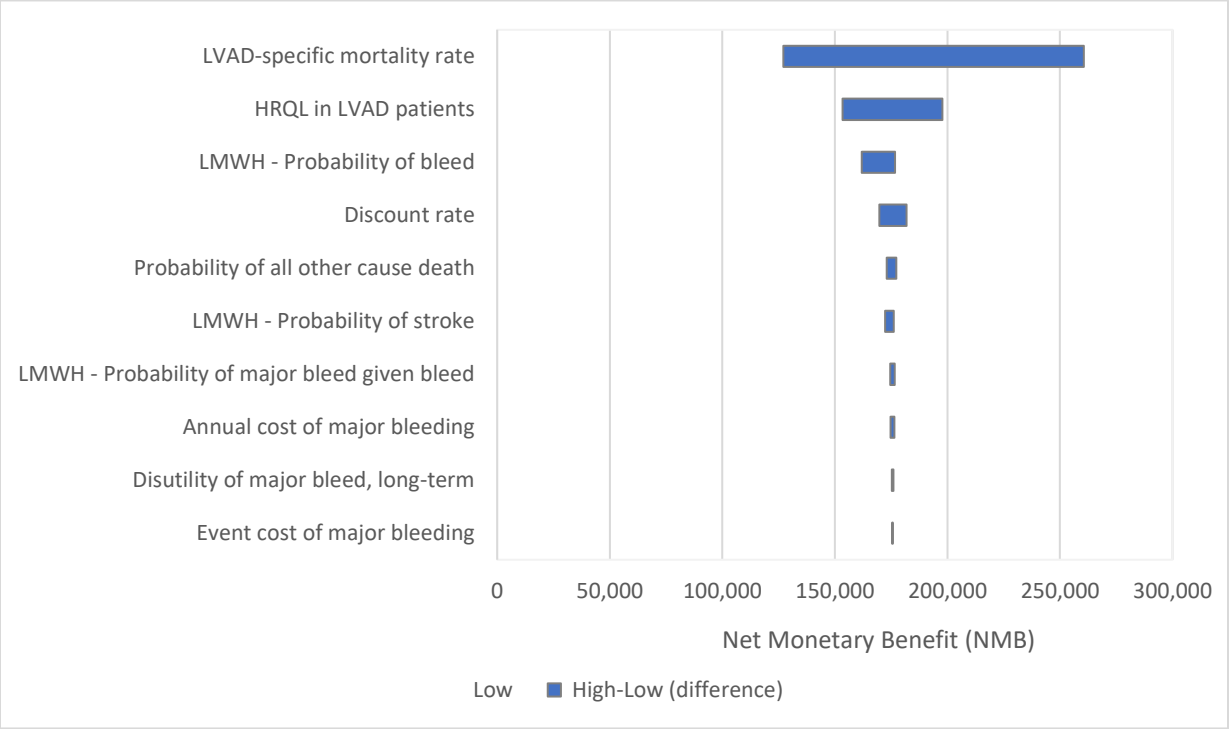


Figure 3.3 Tornado diagram of one-way sensitivity analysis results, low bleed risk patients

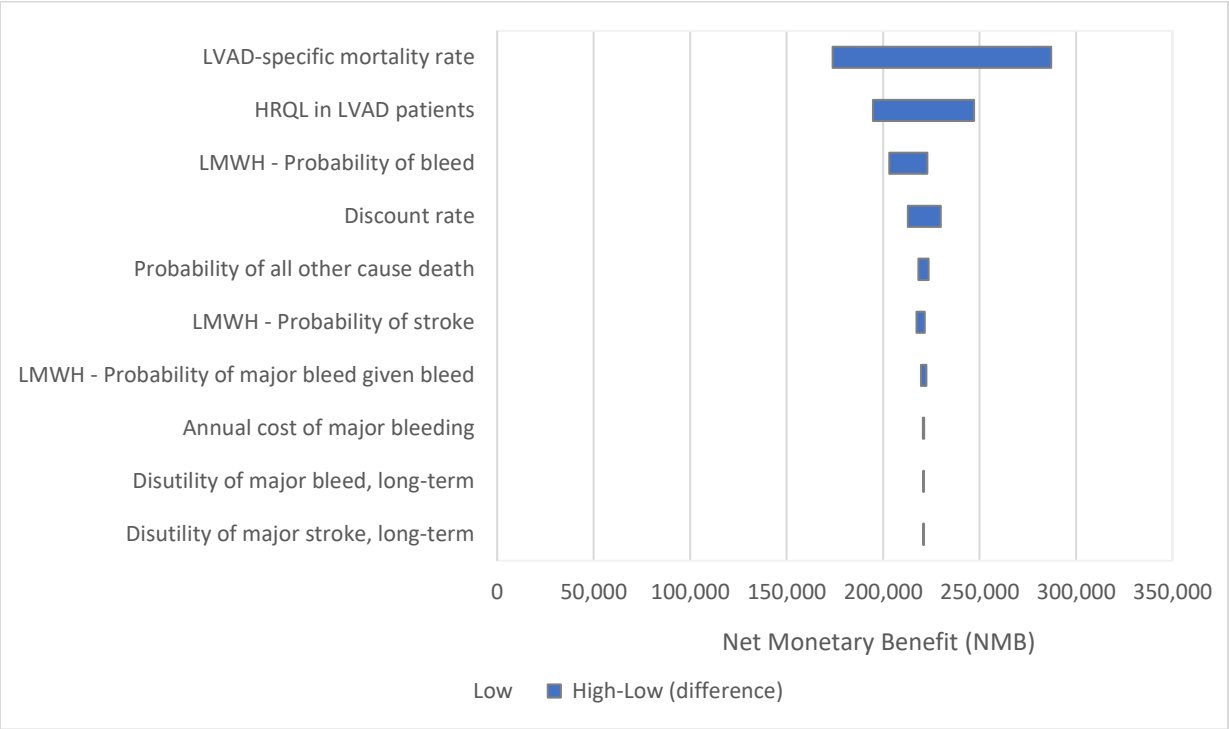
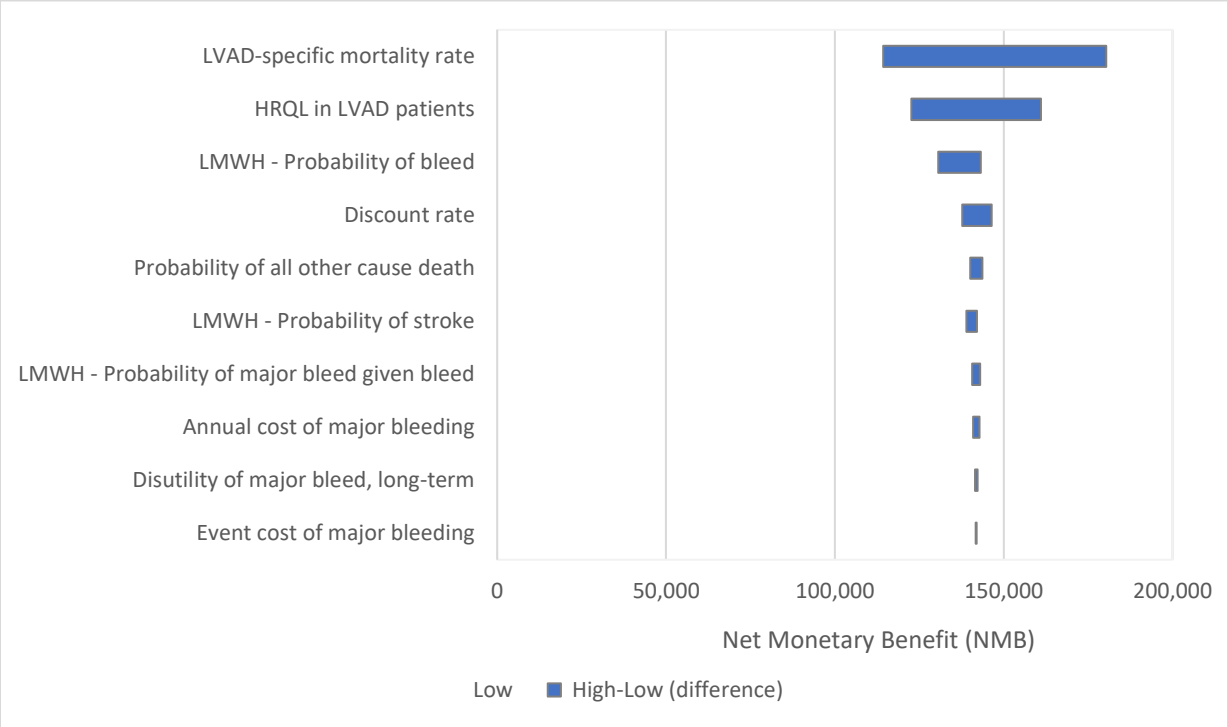


Figure 3.4 Tornado diagram of one-way sensitivity analysis results, high bleed risk patients



The probabilistic sensitivity analysis varied all parameters simultaneously. Figures 3.5-3.7 show cost-effectiveness acceptability curves representing the probability that LMWH is cost-effective for a given maximum WTP threshold per QALY gained for all-risk, low risk, and high risk groups, respectively. With a WTP threshold of $100,000 per QALY, LMWH remained cost-saving in 98.0% of simulations for all-risk patients, 96.6% of simulations for the low-risk group and 98.5% of iterations for the high-risk group.

Figure 3.5 Cost-effectiveness acceptability curve for all risk patients

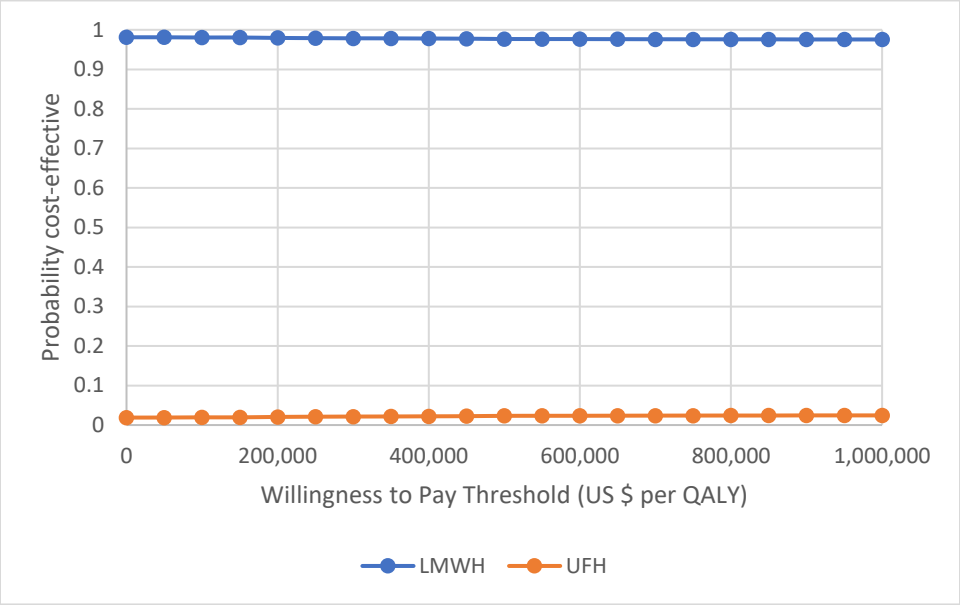


Figure 3.6 Cost-effectiveness acceptability curve for low bleed risk group

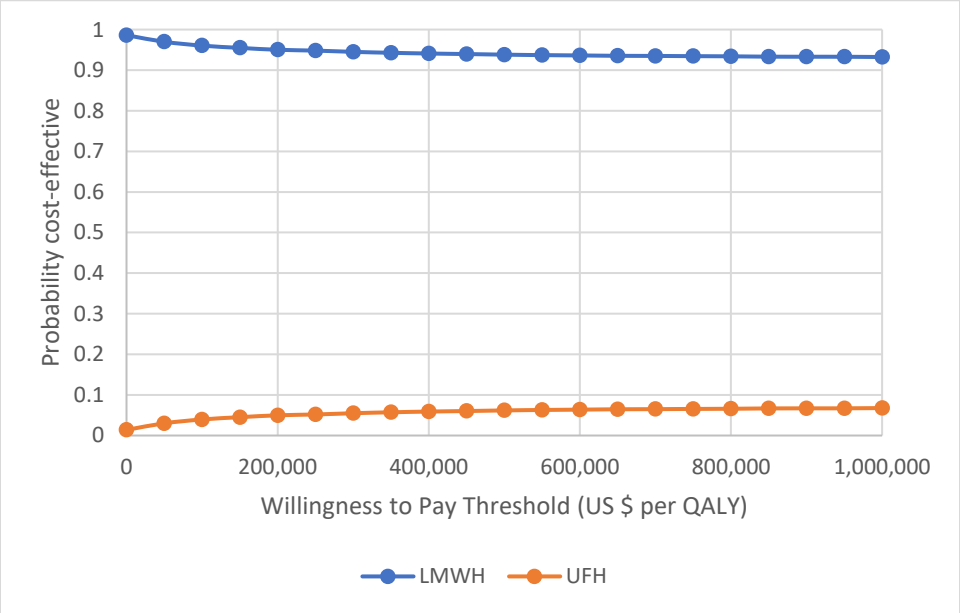
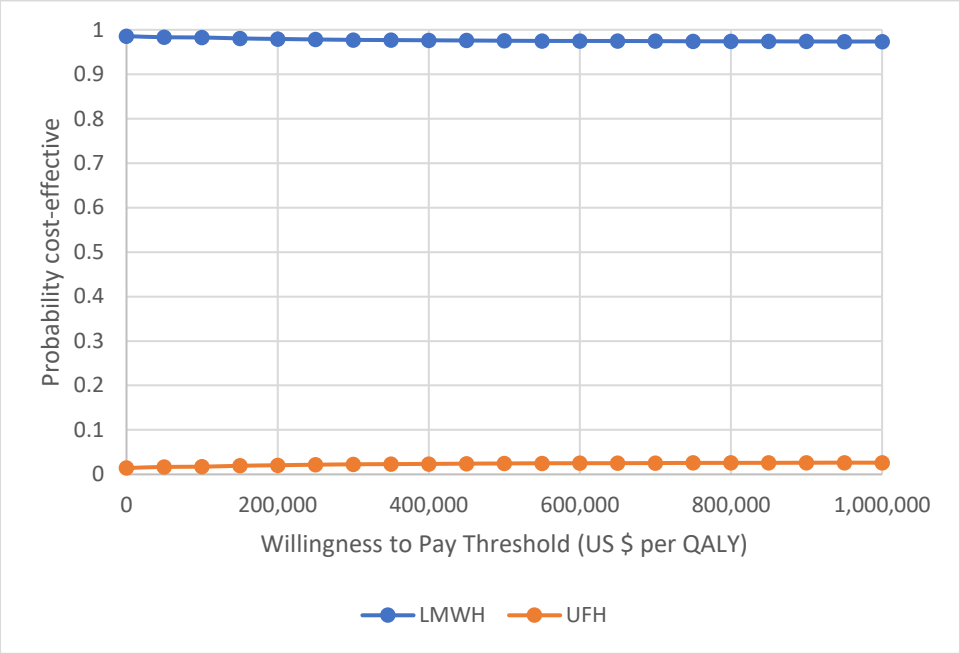


Figure 3.7 Cost-effectiveness acceptability curve for high bleed risk group



3.4 Discussion

We found that outpatient LMWH administration is cost-saving, compared to intravenous UFH therapy, in the chronic therapy phase after hospital discharge following LVAD implantation. These results held for all-risk patients as well as both low- and high-risk groups. Fully implementing LMWH bridging for LVAD patients who are eligible for LMWH at centers that are only or partially using UFH therapy could have large population-level health and cost impacts. Patients and third-party payers could pocket considerable savings from the switch. In addition, as UFH bridging requires an inpatient admission, administering LMWH bridging for eligible patients would free hospital beds for other clinical needs. Policy makers could recommend that payers take steps to incentivize using outpatient LMWH therapy. For example, Medicare could consider increasing the reimbursement for LMWH to make the margins in dollars to healthcare providers for prescribing UFH and LMWH equivalent.

One-way sensitivity analyses showed that the net monetary benefit of LMWH compared with UFH bridging is most sensitive to probability of bleed associated with LMWH bridging for all-risk patients as well as both low and high risk groups. Probabilistic sensitivity analyses revealed that there appears to be little uncertainty that outpatient management with LMWH is cost-saving than inpatient UFH bridging in LVAD patients. But, the probability that UFH is cost-effective was higher in the low-risk group than in the high-risk group, suggesting that it is more ambiguous that LMWH is better for low-risk patients. A future scientific study adequately powered to detect whether rates of side effects, such as bleeding, differ between these two bridging anticoagulation strategies across risk groups could be valuable.

Our study does have some limitations. To begin, the adverse event rates are based on a retrospective cohort study of only two centers and a relatively small sample size. As such, there is uncertainty in the model inputs. In addition, LVAD patients with advanced renal disease are not eligible for LMWH bridging [18], and we do not have data on this subset of patients. Further, we did not have data on some parameters, such as LVAD-specific mortality, by age. We assumed that LVAD-specific mortality is the same across ages 18-82, but it is plausible that LVAD-specific mortality differs by age.

Another limitation is that we did not incorporate societal spillover effects to caregivers of LVAD patients due to a lack of literature on health utility values and productivity costs associated with being a caregiver of an LVAD patient. The potential impact of including spillover effects on the societal costs of LMWH vs. UFH is ambiguous. Including spillovers effects on caregivers' and family members' utility and productivity could possibly make LMWH bridging less cost-saving, as caregivers could spend time helping administer LMWH injections at the patient's home, which may be inconvenient and time-consuming for the caregivers. Yet,

though qualitative interviews of spousal caregivers of LVAD patients reveal that they had to make sacrifices in terms of employment and their own health and experienced fear and anxiety in caring for their spouse [19], it is doubtful that the potential additional caregiver burden associated with helping administer LMWH injections would be large enough that it would outweigh the $9,680 in incremental costs. Caregivers would have to spend about $97 an hour for 100 hours for LMWH to offset UFH. On the flip side, incorporating caregiver spillover effects could make LMWH bridging more cost-saving, as caregivers may incur higher utility losses and productivity costs if they accompany the patient to the hospital to get intravenous UFH therapy and stay by their bedside.

Future research could examine the budget impact of fully implementing LMWH bridging at centers that are only or partially using UFH therapy. The budget impact analysis would use the disease model from Aim 2 as well as the annual number of bridging episodes in the United States as inputs. We would also need to know current provider practice patterns around the use of LMWH vs UFH bridging anticoagulation for unexpected low INR in ambulatory LVAD patients. Toward this end, we have developed and administered a survey to understand provider practice patterns across a wide range of centers in the United States [Appendix D]. Even in our retrospective cohort study of two hospitals, there is wide variation in practice patterns. At Medical College of Wisconsin, there was a change in management who thought UFH was the optimal bridging anticoagulation strategy, leading to a change in practice at the Medical College of Wisconsin. The budget impact analysis would incorporate the cost of outreach to clinicians regarding the potential benefits for patient safety of using LMWH rather than UFH.

3.5 Conclusion

A lesson from this study for healthcare providers, payers, and policymakers is that bridging anticoagulation for LVAD patients is an easy target for cost savings. There appears to be little uncertainty that outpatient management with LMWH is cost-saving than inpatient UFH bridging in LVAD patients. Yet, as these results are based on data on adverse events associated with use of LMWH vs UFH bridging from a retrospective cohort study of patients cared for in only two medical centers, a future scientific study adequately powered to detect whether side-effect rates differ between these two bridging anticoagulation strategies could be valuable.

3.6 References

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3.7 Appendix

Table 3.A.1 Life table for the total population: United States, 2019 (CEA)

Age	Mortality	Age	Mortality	Age	Mortality
18–19	0.00060	46–47	0.00285	74–75	0.02634
19–20	0.00070	47–48	0.00308	75–76	0.02904
20–21	0.00080	48–49	0.00336	76–77	0.03200
21–22	0.00089	49–50	0.00368	77–78	0.03544
22–23	0.00097	50–51	0.00403	78–79	0.03926
23–24	0.00103	51–52	0.00440	79–80	0.04339
24–25	0.00108	52–53	0.00482	80–81	0.04816
25–26	0.00112	53–54	0.00529	81–82	0.05322
26–27	0.00117	54–55	0.00578		
27–28	0.00121	55–56	0.00628		
28–29	0.00125	56–57	0.00679		
29–30	0.00130	57–58	0.00732		
30–31	0.00135	58–59	0.00787		
31–32	0.00140	59–60	0.00846		
32–33	0.00145	60–61	0.00909		
33–34	0.00151	61–62	0.00977		
34–35	0.00156	62–63	0.01047		
35–36	0.00162	63–64	0.01118		
36–37	0.00168	64–65	0.01192		
37–38	0.00174	65–66	0.01271		
38–39	0.00180	66–67	0.01362		
39–40	0.00186	67–68	0.01462		
40–41	0.00194	68–69	0.01577		
41–42	0.00204	69–70	0.01710		
42–43	0.00216	70–71	0.01843		
43–44	0.00231	71–72	0.02032		
44–45	0.00247	72–73	0.02210		
45–46	0.00265	73–74	0.02419		
Data source: 15					

Table 3.A.2 Life table for the LVAD population overall: United States, 2019 (CEA)

Age	Mortality	Age	Mortality	Age	Mortality
18–19	0.25460	46–47	0.25685	74–75	0.28034
19–20	0.25470	47–48	0.25708	75–76	0.28304
20–21	0.25480	48–49	0.25736	76–77	0.28600
21–22	0.25489	49–50	0.25768	77–78	0.28944
22–23	0.25497	50–51	0.25803	78–79	0.29326
23–24	0.25503	51–52	0.25840	79–80	0.29739
24–25	0.25508	52–53	0.25882	80–81	0.30216
25–26	0.25512	53–54	0.25929	81–82	0.30722
26–27	0.25517	54–55	0.25978		
27–28	0.25521	55–56	0.26028		
28–29	0.25525	56–57	0.26079		
29–30	0.25530	57–58	0.26132		
30–31	0.25535	58–59	0.26187		
31–32	0.25540	59–60	0.26246		
32–33	0.25545	60–61	0.26309		
33–34	0.25551	61–62	0.26377		
34–35	0.25556	62–63	0.26447		
35–36	0.25562	63–64	0.26518		
36–37	0.25568	64–65	0.26592		
37–38	0.25574	65–66	0.26671		
38–39	0.25580	66–67	0.26762		
39–40	0.25586	67–68	0.26862		
40–41	0.25594	68–69	0.26977		
41–42	0.25604	69–70	0.27110		
42–43	0.25616	70–71	0.27243		
43–44	0.25631	71–72	0.27432		
44–45	0.25647	72–73	0.27610		
45–46	0.25665	73–74	0.27819		
Data sources: 15, 16					

Table 3.A.3 Life table for the LVAD population with low bleed risk: United States, 2019 (CEA)

Age	Mortality	Age	Mortality	Age	Mortality
18–19	0.20060	46–47	0.20285	74–75	0.22634
19–20	0.20070	47–48	0.20308	75–76	0.22904
20–21	0.20080	48–49	0.20336	76–77	0.23200
21–22	0.20089	49–50	0.20368	77–78	0.23544
22–23	0.20097	50–51	0.20403	78–79	0.23926
23–24	0.20103	51–52	0.20440	79–80	0.24339
24–25	0.20108	52–53	0.20482	80–81	0.24816
25–26	0.20112	53–54	0.20529	81–82	0.25322
26–27	0.20117	54–55	0.20578		
27–28	0.20121	55–56	0.20628		
28–29	0.20125	56–57	0.20679		
29–30	0.20130	57–58	0.20732		
30–31	0.20135	58–59	0.20787		
31–32	0.20140	59–60	0.20846		
32–33	0.20145	60–61	0.20909		
33–34	0.20151	61–62	0.20977		
34–35	0.20156	62–63	0.21047		
35–36	0.20162	63–64	0.21118		
36–37	0.20168	64–65	0.21192		
37–38	0.20174	65–66	0.21271		
38–39	0.20180	66–67	0.21362		
39–40	0.20186	67–68	0.21462		
40–41	0.20194	68–69	0.21577		
41–42	0.20204	69–70	0.21710		
42–43	0.20216	70–71	0.21843		
43–44	0.20231	71–72	0.22032		
44–45	0.20247	72–73	0.22210		
45–46	0.20265	73–74	0.22419		
Data sources: 15, 16, 17					

Table 3.A.4 Life table for the LVAD population with high bleed risk: United States, 2019 (CEA)

Age	Mortality	Age	Mortality	Age	Mortality
18–19	0.30060	46–47	0.30285	74–75	0.32634
19–20	0.30070	47–48	0.30308	75–76	0.32904
20–21	0.30080	48–49	0.30336	76–77	0.33200
21–22	0.30089	49–50	0.30368	77–78	0.33544
22–23	0.30097	50–51	0.30403	78–79	0.33926
23–24	0.30103	51–52	0.30440	79–80	0.34339
24–25	0.30108	52–53	0.30482	80–81	0.34816
25–26	0.30112	53–54	0.30529	81–82	0.35322
26–27	0.30117	54–55	0.30578		
27–28	0.30121	55–56	0.30628		
28–29	0.30125	56–57	0.30679		
29–30	0.30130	57–58	0.30732		
30–31	0.30135	58–59	0.30787		
31–32	0.30140	59–60	0.30846		
32–33	0.30145	60–61	0.30909		
33–34	0.30151	61–62	0.30977		
34–35	0.30156	62–63	0.31047		
35–36	0.30162	63–64	0.31118		
36–37	0.30168	64–65	0.31192		
37–38	0.30174	65–66	0.31271		
38–39	0.30180	66–67	0.31362		
39–40	0.30186	67–68	0.31462		
40–41	0.30194	68–69	0.31577		
41–42	0.30204	69–70	0.31710		
42–43	0.30216	70–71	0.31843		
43–44	0.30231	71–72	0.32032		
44–45	0.30247	72–73	0.32210		
45–46	0.30265	73–74	0.32419		
Data sources: 15, 16, 17					

Table 3.A.5 Impact Inventory

Sector	*Type of Impact (list category within each sector with unit of measure if relevant*)*	*Included in This Reference Case Analysis from … perspective?*		*Notes on Sources of Evidence*
		Healthcare Sector	*Societal*	
Formal Healthcare sector				
Health	*Health outcomes (effects)*			
	Longevity effects	☑	☐	
	Health-related quality-of-life effects	☑	☐	Utility Weight
	Other health effects (e.g., adverse events and secondary transmissions of infections)	☐	☐	
	Medical costs			
	Paid for by third-party payers	☑	☐	
	Paid for by patients Out-of-pocket	☑	☐	
	Future related medical costs (payers and patients)	☑	☐	
	Future unrelated medical costs (payers and patients)	☐	☐	
Informal Healthcare sector				
Health	Patient time costs	NA	☐	Not included and listed as limitation

	Unpaid caregiver time costs	NA	☐	Not included and listed as limitation
	Transportation costs	NA	☐	
Non-healthcare sectors (with examples of possible items)				
Productivity	Labor market earnings lost	NA	☐	LVAD patients typically are unable to work due to disability
	Cost of unpaid lost productivity due to illness	NA	☐	
	Cost of uncompensated household production	NA	☐	
Consumption	Further consumption unrelated to health	NA	☐	
Social services	Cost of social services as part of intervention	NA	☐	
Legal/criminal justice	Number of crimes related to intervention	NA	☐	
	Cost of crimes related to intervention	NA	☐	
Education	Impact of intervention on educational achievement of population	NA	☐	
Housing	Cost of intervention on home improvements (e.g., removing lead paint)	NA	☐	
Environment	Production of toxic waste or pollution by intervention	NA	☐	
Other (specify)	Other impacts	NA	☐	
*Categories listed are intended as examples for analysts. Abbreviation: NA = Not applicable				

Table 3.A.6 Projected Probabilities of Adverse Events, By Risk Status and Overall

	Probability of minor bleed	**Probability of major bleed**	**Probability of minor stroke**	**Probability of major stroke**
All-risk patients				
UFH	0.0021	0.0292	0.0095	0.0005
LMWH	0.0071	0.0070	0.0001	0.0010
Low bleed risk group				
UFH	0.0018	0.0325	0.0095	0.0005
LMWH	0.0044	0.0022	0.0001	0.0018
High bleed risk group				
UFH	0.0024	0.0268	0.0095	0.0005
LMWH	0.0090	0.0086	0.0001	0.0001

Table 3.A.7 Disaggregated Costs in the Base Case, By Risk Status and Overall

	INR Monitoring Costs, $	**Bridging Anticoagulation Costs, $**	**Adverse Event Costs, $**
All-risk patients			
UFH	75.95	5,108	6,262
LMWH	75.95	273	1,416
Low bleed risk group			
UFH	75.95	5,108	7,104
LMWH	75.95	273	832
High bleed risk group			
UFH	75.95	5,108	5,834
LMWH	75.95	273	1,470

Chapter 4 Value of Information Analysis Optimizing Future Trial Design

Abstract

Patients with left ventricular assist devices (LVAD) often require temporary "bridging" anticoagulation to prevent life-threatening thromboembolic complications. Given a lack of clinical trial data, bridging practice varies widely between different LVAD centers. This study quantified the potential value of a future trial assessing adverse events in patients treated with LMWH vs UFH.

Expected value of perfect, partial perfect and sample information (EVPI, EVPPI and EVSI) analyses were conducted using a probabilistic model. EVSI was quantified with net monetary benefit (assuming willingness to pay for health as $100,000/QALY). We calculated discounted population-level EVSI by multiplying per-episode EVSI by the annual number of bridging procedures in the United States and assuming a 10-year time frame over which improved anticoagulation would be used. Study costs were based on administrative costs and bridging anticoagulation costs.

The discounted population-level EVPI and EVPPI were $5.6 million and $2.8 million, respectively. Though the VOI from future trials collecting data on adverse event rates was outweighed by the costs of these trials across study sample sizes, we found that a database study collecting longitudinal data on 30-day outcomes in patients bridged for low INR could be valuable. The optimal patient enrollment of a database study would be 1,000 with expected population-level societal returns (EVSI minus study costs) of $687,000.

4.1 Introduction

Healthcare decision makers need to determine the expected payoffs associated with each decision. The results of cost-effectiveness analyses (CEAs) are surrounded by uncertainty as the available information about costs and effectiveness of healthcare interventions is rarely perfect [1]. This decision uncertainty confers a risk of adopting suboptimal interventions [2]. Given constraints on US health care resources, these suboptimal decisions will result in higher costs and health loss. Although uncertainty in decision making can be decreased with additional information, conducting additional research may not be worthwhile given the high costs of research studies. Therefore, it is reasonable to assess the value of additional research before making decisions [3].

Value of information (VOI) analysis is based on the principle that improved outcomes could be achieved with a different decision if more information were available. VOI is a Bayesian analytical framework for the identification and adoption of the alternative with the maximum expected net benefit [4]. A VOI analysis estimates the expected value of research in reducing the uncertainty around cost-effectiveness estimates [1,4]. This value can be compared with the study costs of acquiring the information to assist policy makers in deciding whether it is worthwhile. The VOI also informs which specific model parameters may benefit the most from additional research [1,2].

We found from Aim 2 that it is highly unlikely that event rates with LMWH would be high enough for it to not be cost-effective compared to UFH. Yet, our event rates were based on a retrospective, observational analysis of patients cared for in only two medical centers and may be biased by unobserved confounding. Therefore, in this study, we conducted VOI analyses to quantify the potential value of a future clinical trial comparing UFH and LMWH bridging in

LVAD patients and to determine the optimal design of such a trial. In addition, we identified the impact of key parameters—risk of adverse events, health utility weights, and utilization of resources—on the uncertainty.

4.2 Methods

Expected value of perfect, partial perfect and sample information (EVPI, EVPPI and EVSI) analyses were conducted, using the decision tree model from Aim 2. Appendix Table 1 shows the list of parameter inputs used in the model. Parameter estimates of differential rates of bleeding and thrombotic events and deaths conditional on receiving LMWH vs UFH therapy and uncertainty ranges were derived from analysis of the data from our retrospective cohort study and data from Shah et al. [5]. Costs and health utilities were derived from published studies. We used probabilistic Monte Carlo simulation to calculate the expected value of additional information.

Expected Value of Perfect Information

The EVPI is the difference between the expected value of a decision made with perfect information about all the uncertain parameters and a decision made under the current conditions of uncertainty. It places an upper bound on the value of future trials. We characterized EVPI using net monetary benefit (NMB), a metric that quantifies overall value to society by subtracting costs from monetized health benefits (assuming willingness to pay [WTP] for health as $100,000/QALY). We calculated discounted population-level EVPI by multiplying per-procedure EVPI by the annual number of bridging procedures in the United States and assuming a 10-year time frame over which improved anticoagulation would be used. An annual discount rate of 3% was used.

Calculating Annual Number of Bridging Procedures

We estimated the annual number of bridging procedures in the United States in the ambulatory setting from the annual number of LVAD implantations, time out of therapeutic range per patient, the number of bridging episodes per patient per year and the mean number of years patients live. As there were 3,198 LVAD implantations in 2019 [6], we projected that there may be 3,500 LVAD implantations in 2022. Using data from the retrospective cohort study, we found that LVAD patients have, on average, 2 bridging episodes for subtherapeutic INR per year and the average duration of follow-up per patient (from LVAD implantation to last bridging episode) is 1.5 years. Therefore, we estimated that there are about 10,500 annual bridging decisions, including decisions for new patients and for patients from the previous year who are continuing to be bridged. As about 10% of LVAD patients have advanced renal disease [7] and are contraindicated for LMWH administration due to a concern that LMWH will accumulate [8], we determined that 90% of bridging procedures might switch, yielding an annual number of bridging procedures of 9,450 for our VOI analyses.

Expected Value of Partial Perfect Information

The EVPPI calculates the expected value of perfect information of individual parameters or groups of parameters and enables the identification of parameters with the highest informational value [9]. EVPPI represents the value of resolving current uncertainties surrounding individual or specific groups of input parameters and establishes a theoretical upper bound on the value of further research. The model parameters were grouped into three categories: 1) costs associated with bleeding and thrombotic complications, 2) utilities

associated with bleeding and thrombotic complications, and 3) probabilities of bleeding and thrombotic complications. We took the difference between the per-procedure expected value of a decision made with perfect information about the parameter group and the per-procedure current optimal decision (with uncertainty) to calculate the per-procedure EVPPI for the different parameter groups. We calculated discounted population-level EVPPI by multiplying per-procedure EVSI by the annual number of bridging procedures in the United States and assuming a 10-year time frame over which improved anticoagulation would be used. An annual discount rate of 3% was used.

Expected Value of Sample Information and Expected Net Benefit of Sampling

The EVSI is the difference between the expected value of a decision made with the information from a new trial with a finite sample size and the expected value of a decision on the basis of current information. Similar to EVPPI, the EVSI can be determined for a particular parameter group with remaining uncertain parameters in the model. We calculated the EVSI that will be obtained from reducing uncertainty through collecting data on adverse event rates associated with LMWH and UFH bridging in a new trial. The EVSI was quantified with net monetary benefit (assuming WTP for health as $100,000/QALY). We calculated discounted population-level EVSI by multiplying per-procedure EVSI by the annual number of bridging procedures in the United States and assuming a 10-year time frame over which improved anticoagulation would be used. An annual discount rate of 3% was used.

The expected net benefit of sampling (ENBS) is the difference between the population-EVSI and the total cost for a future research study. We plotted the ENBS as a function of study sample size. The study is valuable when ENBS is positive (i.e., the expected benefits exceed

the expected costs) [3]. The optimal sample size of a future trial would be the one that maximizes the ENBS. In the base-case analysis, we assumed a WTP for health of $100,000/QALY, but also assumed WTP values of $50,000/QALY and $150,000/QALY in sensitivity analyses to examine how the VOI for this treatment decision varies with societal WTP for health.

Calculating Study Costs

The total costs of a future trial consist of 1) fixed costs of setting up and conducting the clinical trial, analyzing the data, and reporting the study findings; 2) per-person variable costs of patient enrollment, follow-up, and data collection; and 3) LMWH and UFH bridging costs. In the base-case analysis, we assumed fixed and variable costs of $500,000 and $2,000, respectively [10]. In a sensitivity analysis, we included a scenario in which a large database study, including longitudinal data on each bridging episode for low INR and 30-day outcomes for the life of an LVAD patient, is conducted. The database study has fixed and variable costs of $100,000 and $500, respectively, but no LMWH and UFH bridging costs.

4.3 Results

Expected Value of Perfect and Partial Perfect Information

With a WTP threshold of $100,000 per QALY, the costs associated with the decision to use LMWH rather than UFH resulted in a total EVPI of $67 per bridging procedure. With 9,450 annual bridging decisions in the United States assuming a 10-year time frame over which improved anticoagulation would be used, the discounted population-level EVPI was $5.6 million. Appendix Figure 4.1 shows a plot of discounted population-level EVPI as a function of WTP for health.

With a WTP of $100,000/QALY, the EVPPI for probabilities of bleeding and thrombotic complications was $33 per bridging procedure. The discounted population-level EVPPI was $2.8 million. These findings indicate that a new study that would eliminate the uncertainty in probabilities of adverse events could be valuable. Appendix Figure 4.2 shows a plot of discounted population-level EVPPI for this parameter group as a function of WTP for health. As the EVPPI for costs associated with complications and the EVPPI for utilities associated with complications did not add value, costs and utilities associated with adverse outcomes were not considered in the EVSI analyses.

Expected Value of Sample Information and Expected Net Benefit of Sampling

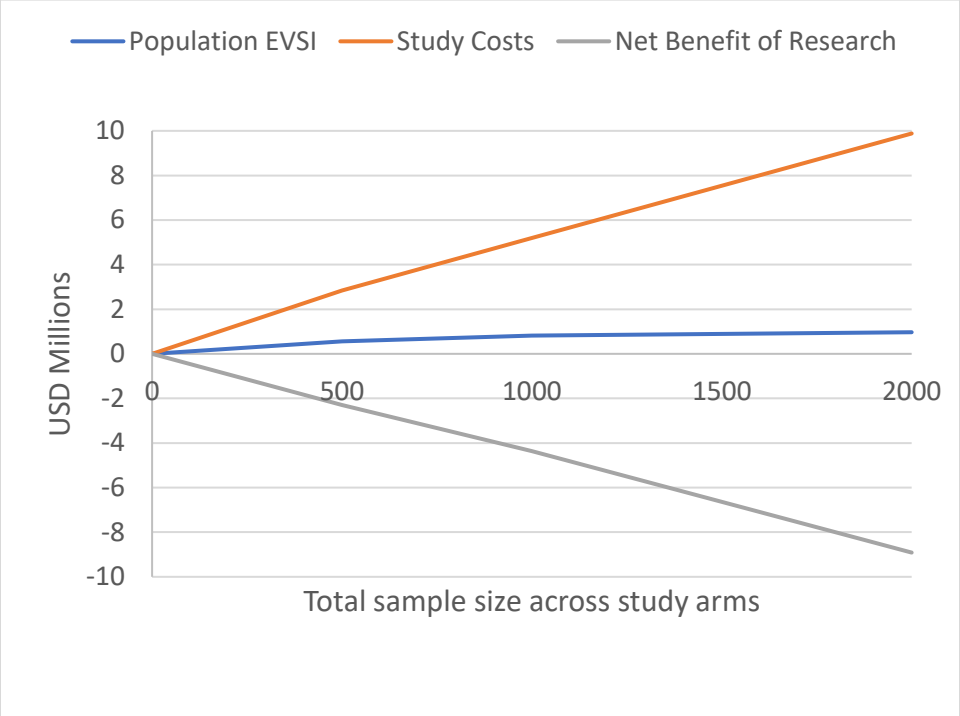
Figure 4.1 demonstrates that the EVSI increases with sample size and approaches the population-level EVPPI ($2.8 million) as the sample size increases. The figure shows a more than twofold variation in the population-level EVSI between WTP thresholds of $50,000/QALY and $150,000/QALY (curves approach an EVPPI of $1.8 million and $3.8 million, respectively). For WTP thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY, the VOI from future trials collecting data on adverse event rates was outweighed by the costs of these trials, yielding negative expected net benefits, across study sample sizes (Figure 4.1).

If a longitudinal database study with fixed and variable costs of $100,000 and $500, respectively, is conducted, enrolling 1,000 LVAD patients would maximize the expected net benefits, with expected population-level societal returns of $687,000, assuming a WTP threshold of $100,000/QALY (Figure 4.2).

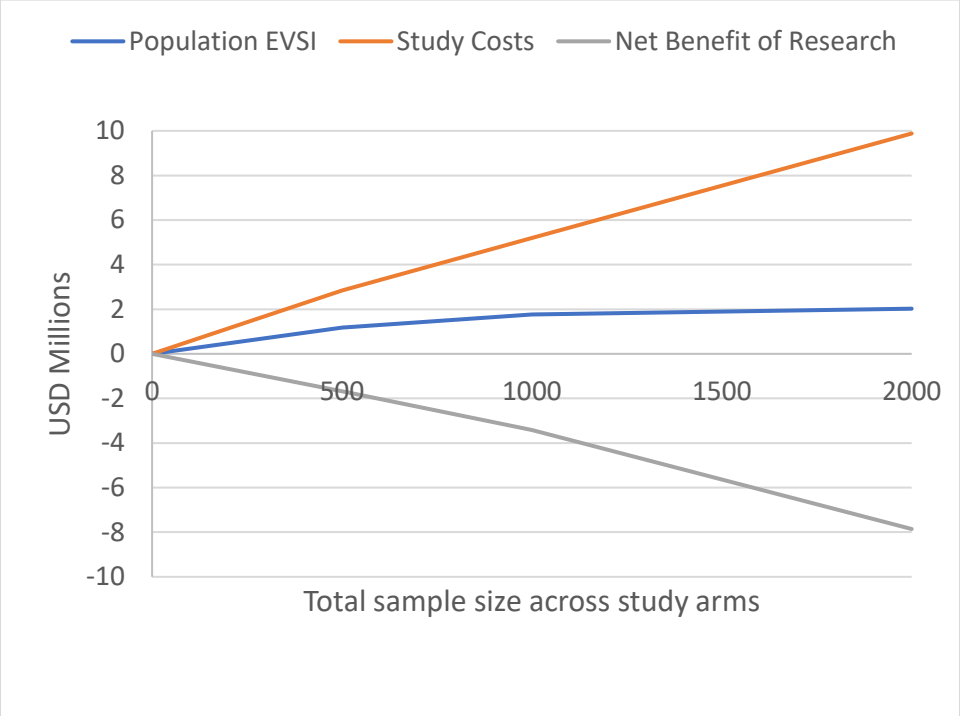
Figure 4.1 EVSI, study costs, and net benefit of new trials for different study sample sizes.

(A) Results for WTP = $100,000/QALY

(B) Results for WTP = $50,000/QALY



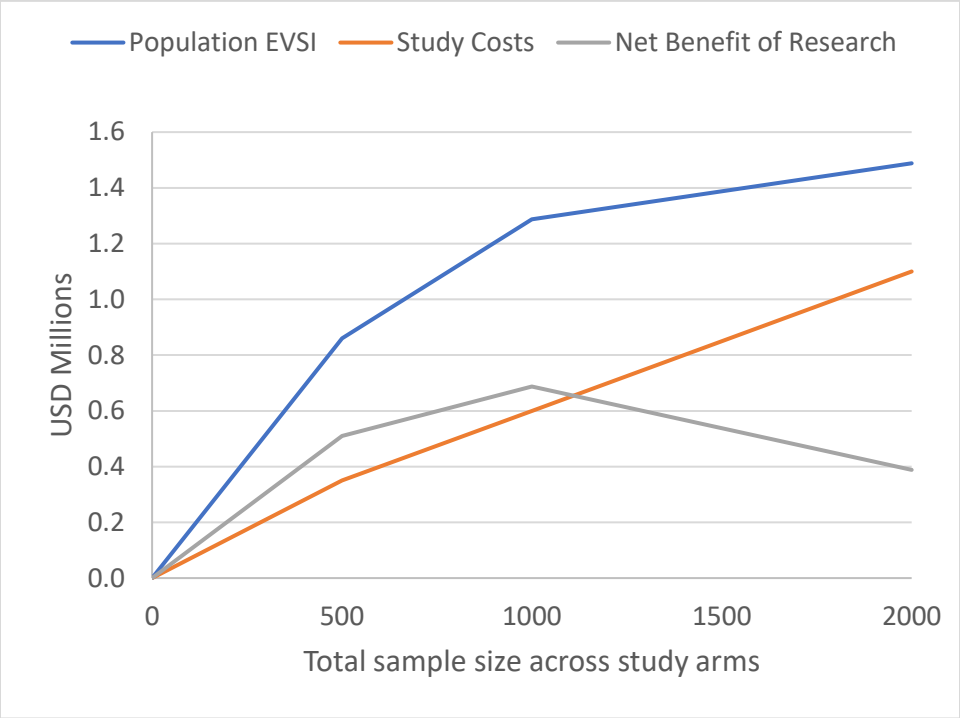
(C) Results for WTP = $150,000/QALY



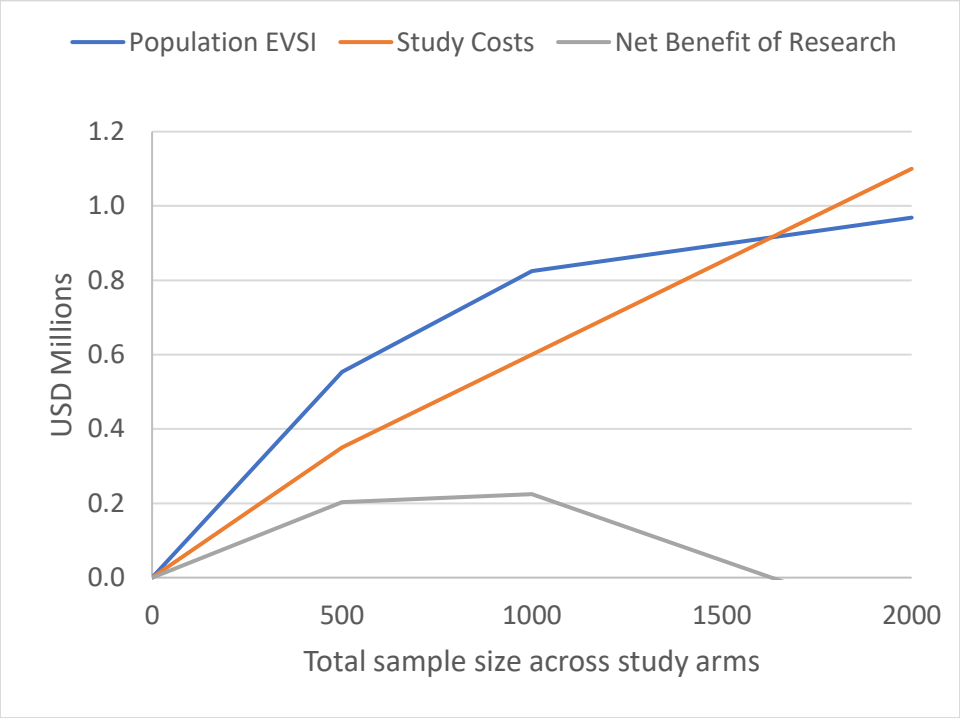
EVSI, expected value of sample information; QALY, quality-adjusted life-year; USD, US dollars; WTP, willingness to pay.

Figure 4.2 EVSI, study costs, and net benefit of a database study for different numbers of patients enrolled

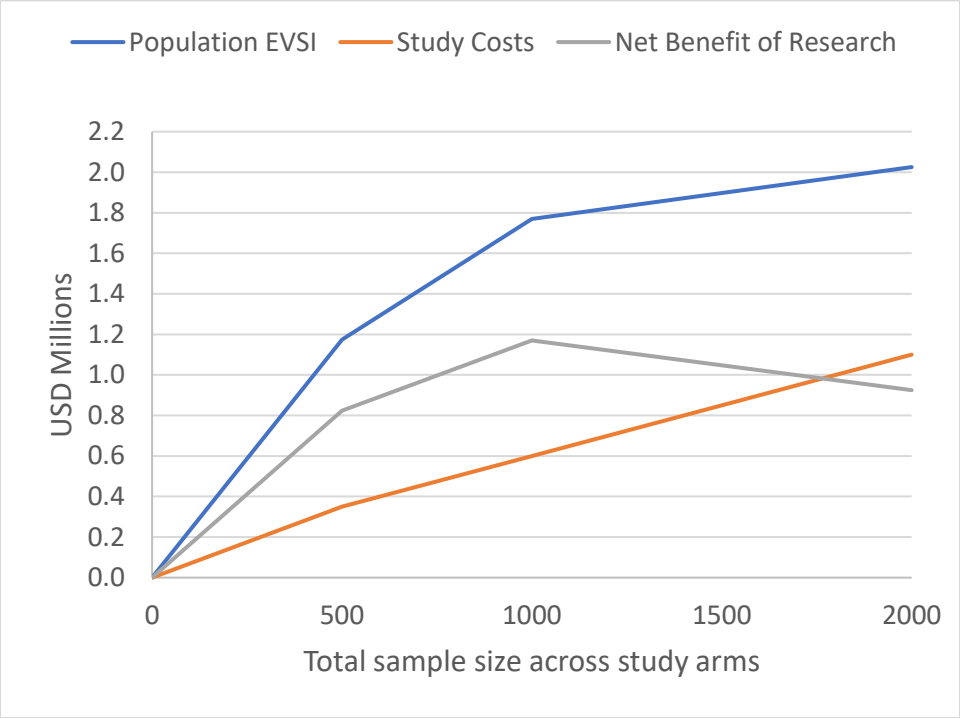
(A) Results for WTP = $100,000/QALY



(B) Results for WTP = $50,000/QALY



(C) Results for WTP = $150,000/QALY



EVSI, expected value of sample information; QALY, quality-adjusted life-year; USD, US dollars; WTP, willingness to pay.

4.4 Discussion

This study found that the population-level EVPPI for probabilities of bleeding and thrombotic outcomes associated with LMWH vs UFH bridging was large at $2.8 million. This highlights the uncertainty in the prior distributions assumed for probabilities of adverse events associated with the bridging strategies. Nevertheless, we found that the value of information from a future trial collecting data on adverse events would be outweighed by the costs of the trial across study sample sizes. Yet, if a database study collecting longitudinal data on 30-day outcomes associated with bridging episodes for LVAD patients were to be conducted, an enrollment of 1,000 patients would be optimal, with expected population-level societal returns (EVSI minus study costs) of $687,000.

Our retrospective cohort study was based on data from fewer than 300 patients across two centers. The statistical uncertainty in the adverse event rates combined with the lifetime mortality, morbidity and cost impacts of bleeding and thrombotic outcomes lead to a situation in which information from a larger database study of LVAD patients bridged for low INR across more centers would be valuable. Confirmation of the hypothesis-generating results from the retrospective cohort study could result in the development of clinical management guidelines for bridging anticoagulation in the ambulatory setting and reduce variation in practice patterns across centers.

A limitation of this study is that the VOI analyses did not incorporate the opportunity cost of spending resources on a trial. Doing so would have reduced the value of additional information, given that the eligible population of LVAD patients with subtherapeutic INR that is not included in the trial might forgo beneficial care awaiting the results [3].

4.5 Conclusion

We used VOI methods to find that expanding research attention to evaluating LMWH vs. UFH bridging anticoagulation for LVAD patients via a larger database study instead of a clinical trial could be justified, assuming that bridging anticoagulation continues to be used over the next 10 years. A database study of 1,000 patients in which more information on adverse event rates is collected would represent good value for information.

4.6 References

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4.7 Appendix

Table 4.A.1 Key model input parameters

Model parameter	Base case	Low	High	Distribution	Data source
Probabilities – LMWH					
Probability of bleed	0.056	0.008	0.104	Beta	Retrospective cohort data, [5]
Probability of major bleed given bleed	0.529	0.292	0.767	Beta	Retrospective cohort data, [5]
Probability of death given major bleed	0.118	0	0.328	Beta	Retrospective cohort data, [5]
Probability of stroke	0.01	0	0.015	Beta	Retrospective cohort data, [5]
Probability of major stroke given stroke	0.95	0.8	1	Beta	Retrospective cohort data, [5], Assumption
Probability of death given major stroke	0.5	0	1	Beta	Retrospective cohort data, [5]
Probabilities – UFH					
Probability of bleed	0.081	0.013	0.149	Beta	Retrospective cohort data, [5]
Probability of major bleed given bleed	0.95	0.8	1	Beta	Retrospective cohort data, [5], Assumption
Probability of death given major bleed	0.25	0	0.55	Beta	Retrospective cohort data, [5]
Probability of stroke	0.01	0	0.019	Beta	Retrospective cohort data, [5]
Probability of major stroke given stroke	0.05	0	0.2	Beta	Retrospective cohort data, [5], Assumption
Probability of death given major stroke	0.05	0	0.2	Beta	Retrospective cohort data, [5], Assumption
Other Probabilities					
Probability of all other cause death	0.168	0.16	0.18	Beta	[10]
LVAD-specific mortality rate	0.254	0.1	0.4	Beta	[16]
Costs (in 2021 US $)					
Cost of intravenous UFH therapy	5,108	4,707	5,544	Nml	[11]

Cost of LMWH bridging	273	268	278	Nml	[12]
Warfarin and international normalized ratio monitoring, monthly	75.95	6.19	145.70	Nml, trunc	[13]
Event cost of minor bleeding	48.71	0	237.90	Nml, trunc	[13]
Event cost of major bleeding	48,651.00	34,870.00	62,435.00	Nml	[13]
Annual cost of major bleeding	40,783.80	2,134.31	79,419.72	Nml	[13]
Event cost of minor stroke	21,532.73	19,135.55	23,931.05	Nml	[13]
Annual cost of minor stroke	11,052.41	2,882.10	19,222.84	Nml	[13]
Event cost of major stroke	34,038.64	30,248.02	37,829.27	Nml	[13]
Annual cost of major stroke	17,469.02	4,540.54	30,383.94	Nml	[13]
Discount rate	0.03	0.01	0.05	Nml, trunc	[3]
Health-utility weights					
HRQL in LVAD patients	0.8	0.7	0.9	Beta	[14]
Disutility of major bleed, long-term	-0.40	-0.20	-0.60	Beta	[13]
Disutility of minor bleed	-0.13	-0.08	-0.13	Beta	[13]
Disutility of major stroke, first year	-0.74	-0.5	-0.8	Beta	[13]
Disutility of major stroke, long-term	-0.29	-0.04	-0.6	Beta	[13]
Disutility of minor stroke	-0.25	-0.15	-0.25	Beta	[13]
Disutility of intravenous therapy	-0.04	-0.02	-0.1	Beta	[7,8]

Figure 4.A.1 Population-level EVPI by WTP

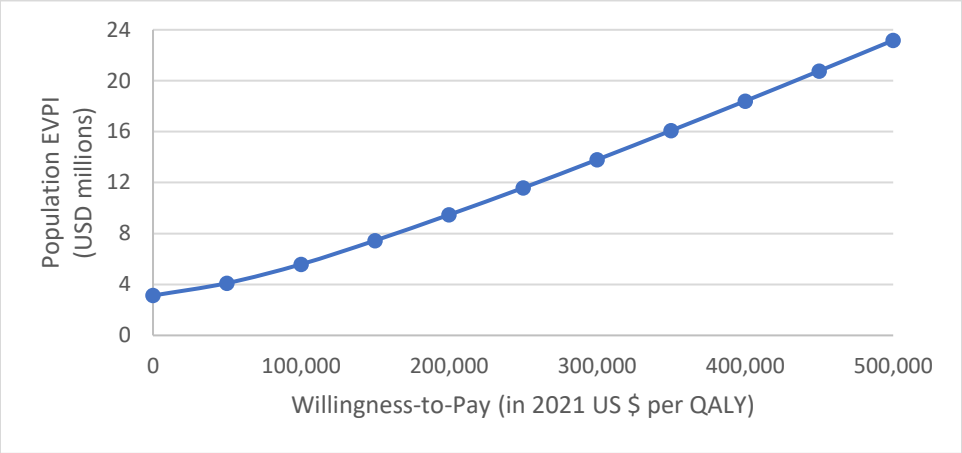
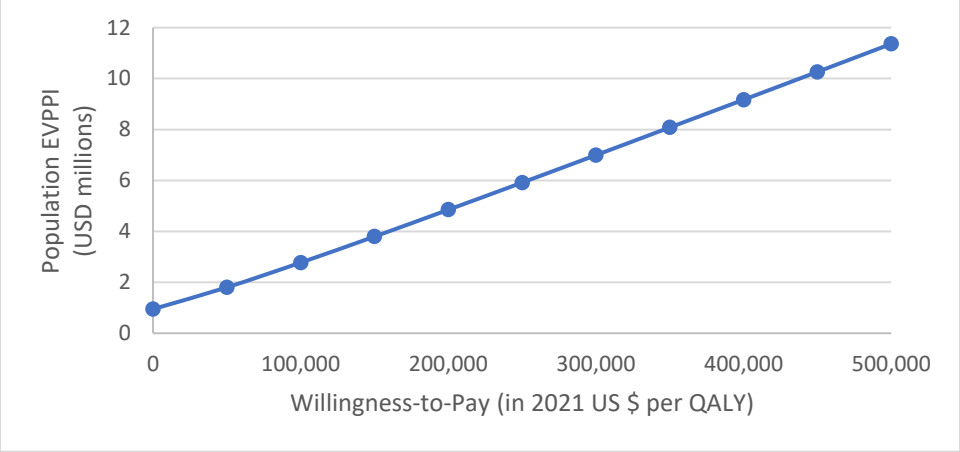


Figure 4.A.2 Population-level EVPPI by WTP



Chapter 5 Conclusion

5.1 Summary

Even in the ambulatory setting following hospital discharge after LVAD implantation, LVAD patients spend more than half of their time with subtherapeutic INR, which can place them at risk for life-threatening thromboembolic complications. Therefore, this is a critical time period to provide optimal anticoagulation bridging to reduce morbidity and mortality.

This dissertation evaluated the comparative effectiveness and cost-effectiveness of outpatient management with low-molecular-weight heparin (LMWH) vs hospitalization with unfractionated heparin (UFH) in the ambulatory setting. We also quantified the potential value of new research assessing adverse events in patients treated with these alternative bridging anticoagulation strategies.

To assess the comparative effectiveness of LMWH vs UFH bridging, we conducted a retrospective cohort study of adults with LVAD implantation between January 2014 and December 2018 from two academic medical centers. Data were collected from 269 patients and 1364 bridging episodes where either UFH or LMWH was administered. Records were reviewed for 30 days after bridging UFH or LMWH was discontinued, assessing for bleeding and/or thromboembolic events. Multivariable logistic regression analysis adjusted for site- and patient-level clustering along with LVAD type and HAS-BLED score for bleed risk. We found that the rate of major bleeding or thromboembolism was non-statistically significantly lower for patients receiving LMWH as compared to UFH. If confirmed in larger, prospective evaluations, this would help to inform decisions on whether to bring LVAD patients with subtherapeutic INR

back for intravenous UFH therapy or bridge with subcutaneous LMWH injection, which can be done at home.

We then projected health and economic outcomes for LMWH vs UFH bridging strategies in all-risk patients as well as both low and high bleed risk groups using a decision analytic model parameterized using data on rates of bleeding and thrombotic events and deaths from the two-center retrospective cohort study of LVAD patients and from the published literature. The primary outcome was the incremental cost-effectiveness ratio in 2021 US dollars per quality-adjusted life year (QALY) gained. Using a healthcare sector perspective, the base-case cost-effectiveness analysis showed that outpatient management with LMWH was cost-saving in all-risk patients as well as both risk groups. In probabilistic sensitivity analyses, LMWH remained cost-saving in 98.0% of simulations for all-risk patients, 96.6% of simulations for the low-risk group and 98.5% of iterations for the high-risk group with a WTP threshold of $100,000 per QALY.

Finally, expected value of perfect, partial perfect and sample information (EVPI, EVPPI and EVSI) analyses were conducted using a probabilistic model. EVSI was quantified with net monetary benefit (assuming willingness to pay for health as $100,000/QALY). We calculated discounted population-level value of information by multiplying per-episode value of information by the annual number of bridging procedures in the United States and assuming a 10-year time frame over which improved anticoagulation would be used. Study costs were based on administrative costs and LMWH/UFH costs. The discounted population-level EVPI and EVPPI were $5.6 million and $2.8 million, respectively. Though the VOI from future trials collecting data on adverse event rates was outweighed by the costs of these trials across study sample sizes, we found that a database study collecting longitudinal data on 30-day outcomes in

patients bridged for low INR could be valuable. The optimal patient enrollment of a database study would be 1,000 with expected population-level societal returns (EVSI minus study costs) of $687,000.

In conclusion, using data on adverse event rates associated with LMWH vs UFH bridging from our retrospective cohort study, we found that there appears to be little uncertainty that outpatient management with LMWH is cost-saving for LVAD patients, as compared to inpatient UFH bridging. Though there is uncertainty in the adverse events associated with the bridging strategies, a trial in which more information on adverse events associated with the bridging strategies is collected would not represent good value for money.

5.2 Future Work

Although anticoagulation is useful in preventing pump thrombosis, too much may increase the risk of bleeding complications, including GI bleeding or hemorrhagic stroke [1]. The optimal LMWH injection dosage and INR at which to initiate bridging remains unknown, with assessment of patient-specific factors including thrombotic and bleeding history needed when initiating outpatient bridging. In addition, as LVAD use increases, so do the number of patients with LVADs who also have kidney disease and are contraindicated for outpatient bridging with LMWH [2]. However, there are only sparse data on how best to care for these patients. A database study collecting longitudinal data on patients bridged for low INR and also information on which patients are ineligible for LMWH bridging due to renal failure would be beneficial. This would enable the comparison of efficacy and safety between the two bridging strategies in the subset of patients who are eligible for LMWH bridging and also across patients with different INR values. There is also a need for research on optimal dosing of LMWH depending on INR value. For example, a half dose may be sufficient for those with higher INR levels.

Furthermore, with improvements in technology, an LVAD may be less likely to thrombose. For example, Heartmate 3 is the newest device with specialized design features that has reduced the rate of disabling stroke and pump thrombosis. Nevertheless, there is a residual risk of both surgical and gastrointestinal bleeding [1], which may be safely and effectively prevented by anticoagulation. There is a need to evaluate the trade-offs between lower rates of thrombosis and risk of bleeding complications in determining the optimal anticoagulation management strategy as devices evolve. We are currently conducting survey research to examine current bridging anticoagulation practice patterns across a wide range of centers in the United States. The survey is also designed to understand how practice patterns may change with new information on risk of major bleeding and as devices become less thrombogenic [Appendix].

5.3 References

1. Lanfear AT, Hamandi M, Fan J, et al. Trends in HeartMate 3: What we know so far. J Card Surg 2020;35:180-187.
2. Roehm B, Vest AR, Weiner DE. Left ventricular assist devices, kidney disease, and dialysis. *Am J Kidney Dis* 2018;71:257-66.

5.4 Appendix

Bridging Anticoagulation Survey

Start of Block: Default Question Block

Q1. For ambulatory LVAD patients managed with warfarin who have an unexpected sub-therapeutic INR (after initial hospital discharge following LVAD implantation), does your program ever utilize heparin/LMWH bridging?

- ○ Yes (1)
- ○ No (2)

IF YES, PLEASE CONTINUE TO Q2.

IF NO, PLEASE SKIP TO THE END OF THE SURVEY AND SUBMIT.

Q2. Does your center have an outpatient protocol in place for optimal anticoagulation bridging in LVAD patients?

- ☐ Yes (1)
- ☐ No (2)

The following questions pertain to ambulatory patients with an unexpected sub-therapeutic INR (after initial hospital discharge following LVAD implantation) who are eligible for LMWH or UFH bridging. Please provide your best estimates.

Q3. What is the INR level below which bridging is initiated for MOST patients?

	1 1 1 1 1 2
Click/tap and drag on the bar to select your answer ()	

Q4. Does use of heparin/LMWH bridging change based on the type of LVAD (i.e., HeartMate 3, HeartMate II, or HeartWare HVAD)?

- ○ Yes (1)
- ○ No (2)

Q5. Which strategy is utilized most frequently for patients with preserved renal function?

- ○ Admit patients to hospital to receive intravenous unfractionated heparin (UFH) (1)
- ○ Continue outpatient status and utilize subcutaneous low molecular weight heparin (LMWH) (2)
- ○ Other (3) _____

Q6. For patients with preserved renal function, approximately what percentage of bridging episodes are LMWH as compared to UFH?

0 10 20 30 40 50 60 70 80 90 100

Click/tap and drag on the bar to select your answer ()	

Q7. Below what level of creatinine clearance/eGFR (in ml/min) do you consider a patient to be contraindicated for LMWH bridging due to severe renal dysfunction?

0 10 20 30 40 50 60

Click/tap and drag on the bar to select your answer ()	

Q8. Please select the TWO most important considerations for physicians at your center as they select between using LMWH vs UFH bridging.

- [ ] Adverse events associated with LMWH vs UFH bridging (1)
- [ ] Contraindication (i.e., kidney failure) (2)
- [ ] Concerns about bleeding (3)
- [ ] Concerns about thrombotic complications (4)
- [ ] Hospital capacity (5)
- [ ] LMWH administration requires training and education of patients on proper injection technique (6)
- [ ] Patient preference for one type of bridging over another (7)
- [ ] We only use one approach to heparin bridging (8)
- [ ] Other (9) _____

Page Break

The following questions are related to hypothetical scenarios about recommending bridging therapies. In all hypothetical scenarios, UFH and LMWH have equivalent rates of thromboembolism when used for bridging therapy. However, each scenario may have different rates of bleeding.

Q9. If there were a well-designed, prospective study that found UFH and LMWH had an equivalent 2% absolute rate of major bleeding, which would be the first-line recommended bridging therapy for your patients with unexpectedly subtherapeutic INR?

- ○ LMWH (1)
- ○ UFH (2)

Q10. In that same hypothetical clinical trial, if absolute rate of major bleeding was lower with LMWH (2%) than UFH (4%), now which would be the first-line recommended bridging therapy for your patients?

- ○ LMWH (1)
- ○ UFH (2)

Q11. If absolute rate of major bleeding was higher with LMWH (4%) than UFH (2%), now which would be the first-line recommended bridging therapy for your patients?

- ○ LMWH (1)
- ○ UFH (2)

The following question is related to thromboembolism risk associated with LVAD implantation.

Q12. With improvements in LVAD technology, annual rates of thromboembolism post-LVAD implantation have dropped. How low would the annual rates of thromboembolism for LVAD patients with subtherapeutic INR have to be for you to stop bridging for subtherapeutic INR values?

	0 5 10 15 20 25 30 35 40 45 50
Click/tap and drag on the bar to select your answer ()	

End of Block: Default Question Block