

Time in Therapeutic Range Significantly Impacts Survival and Adverse Events in Destination Therapy Patients

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The study aim was to examine the impact time in therapeutic range (TTR, International Normalized Ratio [INR] 2.0–3.0) has on survival and adverse events in patients receiving the HeartWare HVAD System in the ENDURANCE and ENDURANCE Supplemental Trials. Evaluable subjects (n = 495) had >1 INR value recorded 1–24 months postimplant and were categorized as: low TTR (10–39%), moderate TTR (40–69%), and high TTR (≥70%). Baseline characteristics, adverse events, and survival were analyzed. Low TTR patients experienced higher rates of major bleeding (1.69 vs. 0.54 events per patient year [EPY]; $p < 0.001$), GI bleeding (1.22 vs. 0.38 EPY; $p < 0.001$), stroke (0.47 vs. 0.17 EPY; $p < 0.001$), thrombus requiring exchange (0.05 vs. 0.01 EPY; $p = 0.02$), infection (1.44 vs. 0.69 EPY; $p < 0.001$), and renal dysfunction (0.23 vs. 0.05 EPY; $p < 0.001$) compared with high TTR. Moderate TTR had higher rates of major bleeding (0.75 vs. 0.54 EPY; $p < 0.001$), thrombus requiring exchange (0.05 vs. 0.01 EPY; $p = 0.007$), cardiac arrhythmia (0.32 vs. 0.24 EPY; $p = 0.04$), and infection (0.90 vs. 0.69 EPY;

$p = 0.001$) compared with high TTR. Two year survival was greater among moderate and high versus low cohorts (Log-rank $p = 0.001$). The significant reduction in morbidity and mortality in destination therapy (DT) HVAD patients with well-controlled TTR (≥70%) emphasizes the importance of vigilant anticoagulation management. *ASAIO Journal* 2022; 68;14–20

Key Words: left ventricular assist device, time in therapeutic range, destination therapy, HVAD

Heart failure (HF) prevalence continues to rise in the United States with an estimated 6.5 million adults afflicted with the disease.¹ Left ventricular assist device (LVAD) therapy for end-stage HF patients has increased over the past decade in both bridge-to-transplant (BTT) patients awaiting heart transplantation and DT patients ineligible for heart transplantation.^{2–5} Because of the need for chronic anticoagulation therapy on LVAD support in tandem with other underlying comorbidities, thromboembolic and hemorrhagic complications remain a common cause of morbidity and mortality in these patients.^{6–9}

Continuous-flow LVADs are typically implanted through the left ventricular apex and move blood systemically via a spinning impeller. The combination of blood-contacting prosthetic material, shear force generated by the spinning impeller, and potential blood stasis around the inflow cannula gives rise to a procoagulant milieu, increasing the risk for thromboembolism.¹⁰ Anticoagulation and antiplatelet therapies are used to mitigate the risk of thromboembolism. However, there is a delicate balance between bleeding and thrombosis that must be met to achieve long-term safety and to avoid hemocompatibility-related adverse events (HRAEs).¹¹

Anticoagulation with vitamin K antagonists (VKA) is the standard of care for minimizing HRAE in LVAD patients and is typically started early in the postoperative phase once surgical bleeding has subsided. Once VKA therapy is initiated, the intensity of therapy is measured by the international normalized ratio (INR) with the standard INR goal of 2.0–3.0. As LVAD patients spend most of their time outside of the hospital setting, it is difficult to determine whether a patient remains within INR goal longitudinally. Rosendaal *et al.*¹² developed a method to determine the amount of time patients remain within the desired INR goal, also known as the time in therapeutic range (TTR). Taking a patient's individual INR results and assuming the change between values is linear, one can determine the percentage of time a patient is within the targeted range between each INR check.^{12,13} Thus, the quality of anticoagulation management can be evaluated by measuring TTR. Evidence has shown an increased risk of both thrombosis and bleeding events when the TTR decreased in the months before these events.^{14,15} A meta-analysis of TTR in LVAD patients revealed a mean TTR of only 46.5%, highlighting the difficulties associated with maintaining goal anticoagulation

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levels and their contribution to the high rates of bleeding and thromboembolic complications.¹⁶

A better understanding of the morbidity and mortality related to the maintenance of TTR remains an important clinical question for LVAD patients. The HeartWare HVAD System (Medtronic, Minneapolis, MN) is a centrifugal flow pump with hybrid magnetic and hydrodynamic suspension of the impeller that was approved by the Food and Drug Administration (FDA) for both BTT and DT indications, as well as both sternotomy and thoracotomy surgical implant approaches.^{17–21} Manufacturer Instructions for Use recommends long-term oral anticoagulation therapy using warfarin, to maintain an INR goal between 2.0 and 3.0, and aspirin, usually 325 mg daily.²² Two multivariable analyses of the HVAD System identified the INR value as an independent risk factor for pump thrombosis (INR < 2.0) and hemorrhagic cerebrovascular accidents (INR > 3.0).^{23,24} The aim of this study was to determine the clinical impact of TTR in patients receiving the HeartWare HVAD System in the ENDURANCE and ENDURANCE Supplemental Trials.

Methods

Study Design and Definitions

The ENDURANCE and ENDURANCE Supplemental Trials have been previously reported.^{19,20} The ENDURANCE Trial was a multicenter, prospective, controlled, randomized, unblinded trial examining the safety and efficacy of the HVAD System compared with a control (HeartMate II Left Ventricular Assist System, HMII, Abbott Inc., Abbott Park, IL) in heart transplant ineligible, end-stage HF patients (n = 296 HVAD patients).¹⁹ The primary endpoint was noninferiority and survival at 24 months alive on originally implanted device, free from disabling stroke, and free from explant for myocardial recovery or transplant. The ENDURANCE Supplemental Trial was a multicenter, prospective, controlled, randomized, unblinded trial to determine the effects of blood pressure management on survival in DT patients with the HVAD System (n = 308 HVAD patients) compared with standard of care in the same control device (HMII).²⁰ In both trials, INR blood tests were captured at baseline preimplant, at index hospitalization discharge, monthly from 1 to 24 months postimplant, and as needed with adverse events, targeting an INR within therapeutic range of 2.0–3.0. Institutional Review Board approval and patient consent were obtained by the participating institutions before patient enrollment in the above listed clinical trials. Both studies were conducted in compliance with FDA regulations for Good Clinical Practices.

Study Sample

A total of 604 HVAD DT patients were analyzed. HeartMate II control subjects were not included in this analysis. Eligible patients (n = 495) were included in the study if they had >1 INR test result recorded 1–24 months postimplant. International normalized ratio values were included in the analysis as reported by the study protocol and included both phlebotomy lab draw and point-of-care testing. Patients were separated into three cohorts based on the percentage of time reported INR values were within the therapeutic range (2.0–3.0): low TTR (10–39% TTR), moderate TTR (40–69% TTR), and high TTR (≥70% TTR). Time in therapeutic range was calculated based on INRs reported from 1 to 24 months postimplant. It is

important to note that out-of-range INRs could be either sub or supratherapeutic per the predefined INR goal range of 2.0–3.0.

Variables

The following baseline characteristics were assessed for each group: age, sex, race, Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile, ischemic HF, history of diabetes mellitus, atrial fibrillation, peripheral vascular disease, coronary artery disease, stroke, transient ischemic attack, hypertension, cardiopulmonary bypass (CPB), and concomitant tricuspid valve repair. The following baseline measurements were assessed for each group: body mass index, blood urea nitrogen, creatinine, total bilirubin, alanine aminotransferase, aspartate aminotransferase, six-minute walk test, as well as the length of intensive care unit (ICU) stay postimplant.

Outcomes

Survival Analysis. Survival was assessed by the Kaplan–Meier method. For all studies, subjects were censored either at time of device explant due to pump exchange or removal for recovery, heart transplant, or at loss to follow up 2 years postimplant.

Adverse Events. Adverse events were defined per the INTERMACS Version 3.0 Adverse Event Definitions and are reported as events per patient years (EPPY) through 2 years postimplant for all groups analyzed. Documented adverse events included major bleeding, stroke, thrombus requiring device exchange, cardiac arrhythmia, major infection, renal dysfunction, and right HF. Additionally, for patients who experienced an HRAE, defined as hemorrhagic cerebrovascular attack (HCVA), ischemic CVA (ICVA), major bleeding, gastrointestinal (GI) bleeding, and thrombus requiring device exchange, from 1 to 24 months postimplant, TTRs in the 60 days before that event were analyzed and compared with the TTR of patients who did not experience the event over the study period.

Statistical Analysis. Descriptive statistics were used to evaluate baseline clinical and demographic characteristics. Results are reported as mean ± SD for continuous variables and as a percentage for binary variables. TTR was calculated using the Rosendaal linear interpolation method expressed as a percentage of observation time.¹¹ Comparisons between the TTR groups were made with a two-sample t test for continuous variables and Fisher's exact test for categorical variables. Adverse events are reported in EPPY and comparisons between the TTR groups were made with Poisson regression. Comparisons between TTR in 60 days before an event compared with TTR without an event were made with the Wilcoxon test. For all analyses, a $p \leq 0.05$ was considered statistically significant. All statistical analyses were performed with SAS v.9.4 software (SAS Institute, Cary, NC).

Results

A total of 604 patients were implanted with the HVAD System in the combined ENDURANCE and ENDURANCE Supplemental trials. After excluding patients who had ≤1 INR value recorded between 1 and 24 months postimplant, 495 patients were eligible, with a total of 9,993 reported INR

results and a median of 23 INR results/patient in the 23 month follow-up period. Mean TTR calculations per patient revealed 53 patients in the low cohort (10–39% TTR), 219 patients in the moderate cohort (40–69% TTR), and 223 patients in the high cohort ($\geq 70\%$ TTR). The percentage of time the INR checks were within or outside of the targeted 2.0–3.0 range was also determined (Table 1). Mean TTRs for each cohort were as follows: low 27.4%, moderate 57.2%, and high 81.3%. Out-of-range INRs within each cohort were a combination of sub and supratherapeutic levels. When INRs fell outside of therapeutic range, they were most commonly below the specified INR goal. Additionally, the correlation between the number of INR checks and reported TTRs indicates a small trend toward an increased number of INR checks with increased TTR (Figure 1). Analysis of the concomitant aspirin therapy postimplant categorized as none, ≤ 81 , 82–324, and ≥ 325 mg revealed relatively even distribution of mean aspirin dosages across the low TTR cohort, with the highest percentage of patients in the 82–324 mg range for the moderate and high TTR cohorts (Table 2).

Comparison of Baseline Characteristics Between High TTR Versus Low TTR and Moderate TTR Patients

Patients in the high TTR cohort were older (64.2 ± 12.0 vs. 60.4 ± 11.8 years; $p = 0.04$), more likely to be white (74.9% vs. 60.4%; $p = 0.04$), had a longer six-minute walk distance (128.7 vs. 88.1 m; $p = 0.05$), and a shorter index ICU stay postimplant (9.5 vs. 14.0 days; $p = 0.03$) compared with patients in the low TTR cohort. Moderate TTR patients were more likely to have hypertension requiring medication (73.5% vs. 64.6%; $p = 0.05$) and were in the ICU for a longer duration postimplant (11.5 vs. 9.5 days; $p = 0.03$) compared with high TTR patients (Table 3).

Comparisons of baseline characteristics between low TTR and moderate TTR cohorts can be found in Table 1, Supplemental Digital Content 1, <http://links.lww.com/ASAIO/A705>.

Table 1. Percentage of TTR Versus Sub or Supratherapeutic Ranges per Study Cohort 1–24 Months Postimplant

TTR Cohort	INR < 2.0	INR 2.0–3.0	INR > 3.0
Low TTR (10–39%)	57.9%	27.4%	14.8%
Moderate TTR (40–69%)	24.4%	57.2%	18.5%
High TTR ($\geq 70\%$)	12.1%	81.3%	11.0%

TTR, time in therapeutic range.

Comparison of Adverse Events Between High TTR Versus Low TTR and Moderate TTR Patients

Patients in the High TTR cohort had significantly lower 2 year rates of major bleeding (0.54 vs. 1.69 EPPY; $p < 0.001$), GI bleeding (0.38 vs. 1.22 EPPY; $p < 0.001$), HCVA (0.05 vs. 0.19 EPPY; $p < 0.001$), ICVA (0.12 vs. 0.28 EPPY; $p = 0.002$), thrombus requiring exchange (0.01 vs. 0.05; $p = 0.02$), major infection (0.69 vs. 1.44 EPPY; $p < 0.001$), renal dysfunction (0.05 vs. 0.23 EPPY; $p < 0.001$), and right HF (0.15 vs. 0.25, $p = 0.04$), when compared with patients in the low TTR cohort.

Patients in the high TTR cohort had significantly lower 2 year rates of major bleeding (0.54 vs. 0.75 EPPY; $p < 0.001$), thrombus requiring exchange (0.01 vs. 0.05 EPPY; $p = 0.007$), cardiac arrhythmia (0.24 vs. 0.32 EPPY; $p = 0.04$), ventricular arrhythmia (0.14 vs. 0.22 EPPY; $p = 0.009$), and major infection (0.69 vs. 0.90 EPPY; $p = 0.001$) when compared with patients in the moderate TTR cohort (Table 4).

Comparisons of adverse events between low TTR and moderate TTR cohorts can be found in Table 2, Supplemental Digital Content 2, <http://links.lww.com/ASAIO/A706>. Of note, subanalysis of postimplant mean arterial blood pressure (MAP) revealed no significant differences among the three cohorts during the 24 month follow-up (Table 5).

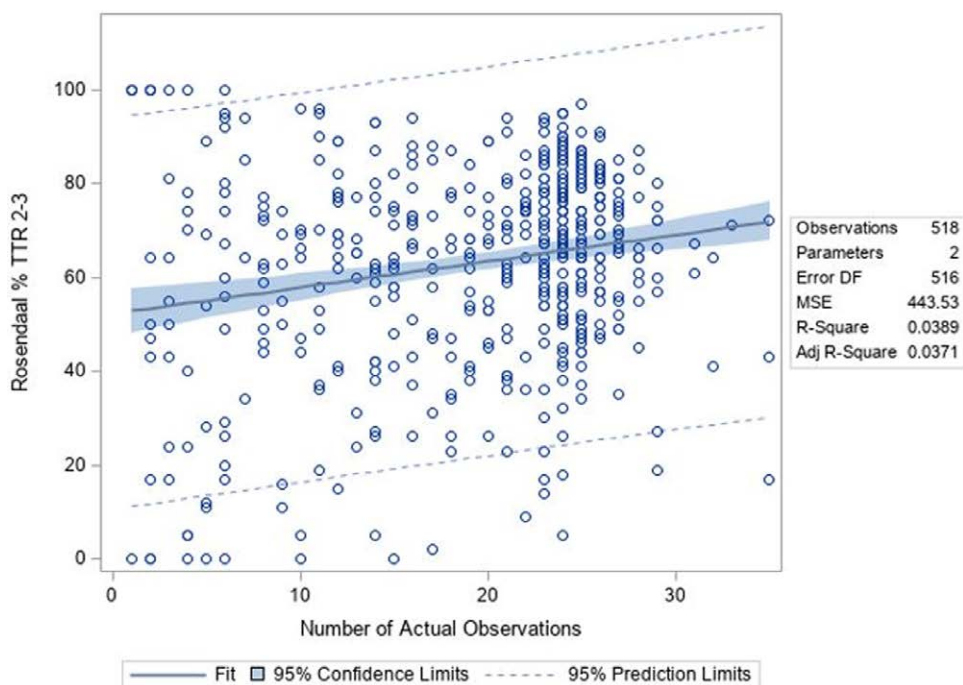


Figure 1. Fit plot: Number of INR Checks versus TTR 2.0–3.0. TTR, time in therapeutic range

Table 2. 1–24 Months Postimplant Mean Daily Aspirin Dose by TTR Cohort

TTR Cohort	Mean Daily Aspirin Dose			
	No ASA	≤81 mg	82–324 mg	≥325 mg
Low (10–39%)	24.5%	28.3%	26.4%	20.8%
Moderate (40–69%)	16.8%	17.7%	40.5%	25.0%
High (≥70%)	23.8%	11.2%	35.4%	29.6%

ASA, acetylsalicylic acid (aspirin); TTR, time in therapeutic range.

TTR Before HRAEs

It has been suggested that falling out of the therapeutic INR range may be a critical factor preceding an HRAE.¹⁹ Therefore, TTRs in the 60 days before a specific HRAE were compared with TTR from 1 to 24 months post-LVAD implant of patients who did not experience an HRAE. For those individuals who experienced an HCVA, the TTR in the 60 days leading up to the event was significantly lower than for those patients who did not have an HCVA (46.3 ± 34.9 vs. 64.0 ± 21.6 , $p < 0.001$). Further analysis revealed that within 60 days of an HCVA, reported INRs were subtherapeutic 32.5% of the time and suprathreshold 21.2% of the time (Tables 6 and 7).

Similarly, for patients who experienced an ICVA, the TTR in the 60 days leading up to the event was lower than for those patients who did not have an ICVA (62.7 ± 37.8 vs. 63.0 ± 21.9 ; $p = 0.05$), with subtherapeutic INRs 20.8% of the time, and suprathreshold INR 16.5%. The TTR in the preceding 60 days before all other types of HRAE (GI bleeding, major bleeding, pump thrombus, and pump exchange due to thrombus) was not significantly different when comparing to the average follow-up TTR in patients who did not have an HRAE (Tables 6 and 7).

Survival

Kaplan–Meier survival analysis at 24 months postimplant between the low TTR compared with the moderate and high TTR groups was statistically different (low TTR: 61.7% versus moderate TTR: 72.4% and high TTR: 75.1%; log-rank $p = 0.001$). Survival was not different between moderate and high TTR groups (Figure 2).

Discussion

This retrospective analysis suggests that consistently maintaining patients on the HVAD System within a prespecified INR goal range of 2.0–3.0 significantly improves survival and reduces adverse events. These adverse events, both non-HRAE and HRAEs, are often the result of the inability to maintain an appropriately anticoagulated state. This state depends on a patient's response to anticoagulant therapy and can be disrupted by the presence of underlying conditions. Clinical management of anticoagulation in patients with infection, RV failure, renal failure, or liver dysfunction, which are often present in LVAD patients, may jeopardize the ability to maintain a therapeutic INR level. Furthermore, anticoagulation strategies and standardized protocols are vital to maintain a high TTR and to prevent potentially life-altering complications that remain the Achilles heel of LVAD therapy. It has been suggested that a TTR <60% should be defined as poorly-controlled anticoagulation treatment for LVAD populations.²⁵ Evidence from our review supports this finding as patients who achieved an even moderate TTR (40–69%) demonstrated an increase in adverse events, including major bleeding and thrombus requiring pump exchange, compared with those with TTR ≥70%. Therefore, measuring and tracking an individual patient's TTR can provide clinical benefit.

Table 3. Baseline and Perioperative Characteristics of Patients in Low, Moderate, and High TTR Cohorts

Baseline Characteristics	Low TTR 10–39% (N = 53)	Moderate TTR 40–69% (N = 219)	High TTR > 70% (N = 223)	p (Low vs. High)	p (Moderate vs. High)
Age (years)*	60.4 ± 11.8	62.6 ± 11.2	64.2 ± 12.0	0.04	0.14
Female	20.8%	21.9%	21.1%	>0.99	0.91
White	60.4%	71.7%	74.9%	0.04	0.45
BMI (kg/m ²)*	28.2 ± 6.8	28.2 ± 5.9	27.5 ± 5.9	0.40	0.18
Diabetes mellitus	45.3%	49.3%	43.9%	0.88	0.29
Atrial fibrillation	52.8%	52.5%	49.8%	0.76	0.57
Peripheral vascular disease	11.3%	10.5%	10.3%	0.81	>0.99
Carotid artery disease	7.5%	12.3%	15.7%	0.19	0.34
Stroke/TIA	17.0%	18.3%	16.6%	>0.99	0.71
Ischemic Heart Failure	60.4%	52.5%	53.4%	0.44	0.92
Hypertension, requiring medication	73.6%	73.5%	64.6%	0.26	0.05
BUN (mg/dl)*	26.5 ± 17.6	27.3 ± 13.7	25.8 ± 11.6	0.86	0.36
Creatinine (mg/dl)*	1.2 ± 0.4	1.4 ± 0.5	1.3 ± 0.4	0.21	0.10
Total bilirubin (mg/dl)*	0.9 ± 0.5	1.1 ± 0.7	1.0 ± 0.6	0.31	0.73
ALT (U/L)*	29.3 ± 18.4	38.1 ± 40.4	35.5 ± 42.2	0.11	0.50
AST (U/L)*	29.5 ± 11.7	32.7 ± 22.5	31.4 ± 21.5	0.39	0.51
Intermacs 1	7.5%	3.7%	2.2%	0.07	0.41
Intermacs 2	30.2%	27.4%	32.3%	0.87	0.30
Intermacs 3	39.6%	44.3%	44.4%	0.54	>0.99
Intermacs 4–7	22.6%	23.7%	20.6%	0.71	0.49
6MWT (m)*	88.1 ± 116.8	104.1 ± 127.6	128.7 ± 141.6	0.05	0.06
Perioperative characteristics					
CPB (minutes)*	91.2 ± 37.5	83.0 ± 38.8	88.9 ± 45.0	0.73	0.14
Concomitant tricuspid repair	26.4%	13.7%	16.6%	0.12	0.43
ICU length of stay (days)*	14.0 ± 14.1	11.5 ± 11.0	9.5 ± 6.7	0.03	0.03

*Value provided as mean ± SD.

6MWT, six-minute walk test; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CPB, cardiopulmonary bypass; ICU, intensive care unit; TIA, transient ischemic attack; TTR, time in therapeutic range.

Table 4. Adverse Events Reported as Events per Patient Year 1–24 Months Postimplant per TTR Cohorts

Adverse Events	Low TTR 10–39% (N = 53)	Moderate TTR 40–69% (N = 219)	High TTR ≥70% (N = 223)	<i>p</i> (Low vs. High)	<i>p</i> (Moderate vs. High)
Major bleeding	1.69	0.75	0.54	<0.001	<0.001
GI bleeding	1.22	0.46	0.38	<0.001	0.11
Stroke	0.47	0.22	0.17	<0.001	0.16
HCVA	0.19	0.06	0.05	<0.001	0.52
ICVA	0.28	0.16	0.12	0.002	0.21
Thrombus with exchange	0.05	0.05	0.01	0.02	0.007
Cardiac arrhythmia	0.30	0.32	0.24	0.39	0.04
Ventricular tachycardia	0.17	0.22	0.14	0.48	0.009
Infection	1.44	0.90	0.69	<0.001	<0.001
Driveline Infection	0.28	0.21	0.18	0.07	0.41
Renal dysfunction	0.23	0.06	0.05	<0.001	0.63
Right heart failure	0.25	0.16	0.15	0.04	0.57

GI, gastrointestinal; HCVA, hemorrhagic cerebrovascular accident; ICVA, ischemic cerebrovascular accident; TTR, time in therapeutic range.

Table 5. Mean Arterial Pressure per TTR Cohort 1–24 Months Postimplant

Postimplant Follow-Up	Low TTR MAP (Mean ± SD)	Moderate TTR MAP (Mean ± SD)	High TTR MAP (Mean ± SD)	<i>p</i>
3 Months	86.5 ± 13.3	86.5 ± 13.8	84.8 ± 11.1	0.70
6 Months	86.4 ± 8.8	86.3 ± 12.3	84.4 ± 12.6	0.37
12 Months	88.4 ± 9.5	86.6 ± 13.3	85.3 ± 11.0	0.49
18 Months	82.8 ± 9.5	85.3 ± 11.4	85.6 ± 12.5	0.08
24 Months	83.6 ± 11.8	84.9 ± 11.3	85.1 ± 11.7	0.91

MAP, mean arterial pressure; TTR, time in therapeutic range.

Achieving a TTR of ≥70% can be challenging to achieve. This goal requires patient adherence to an individualized medication regimen, follow-up testing, provider attentiveness, and systems that can track TTR. All of these actionable events require a collaborative relationship to exist between patient and provider. Management of VKA and INR checks differ between VAD centers. Dose adjustments may or may not be protocol driven and can be managed by a registered nurse, an advanced practice provider, a pharmacist, or a physician. Frequency of testing can range from daily to monthly, depending on the practice patterns of the specific VAD center coupled with the patient's adherence to these recommendations. In a

Table 6. TTR 60 Days Before Event Versus Overall Mean TTR with No-event

Adverse Event		TTR	<i>p</i>
HCVA	No	64.0 ± 21.6	<0.001
	Yes	46.3 ± 34.9	
ICVA	No	63.0 ± 21.9	0.05
	Yes	62.7 ± 37.8	
Major bleed	No	64.4 ± 21.7	0.54
	Yes	59.0 ± 34.9	
GI bleed	No	64.2 ± 20.9	0.46
	Yes	62.9 ± 33.9	
Pump thrombus	No	61.3 ± 23.9	0.18
	Yes	60.2 ± 38.4	
Exchange due to thrombus	No	62.6 ± 22.6	0.67
	Yes	53.9 ± 40.8	

GI, gastrointestinal; HCVA, hemorrhagic cerebrovascular accident; ICVA, ischemic cerebrovascular accident; TTR, time in therapeutic range.

study comparing a patient self-monitored INR check performed daily to a three times weekly strategy, the increased frequency of POC INR testing improved TTR and was associated with a decrease in HRAEs.²⁵ Therefore, utilization of more frequent POC home INR monitoring may be a platform to improve TTR with proper clinical guidance. This study revealed a slight trend towards increased frequency of INR checks associated with higher TTR (Figure 2). More studies are needed on this aspect of anticoagulation management in this population.

VAD programs should analyze program practices and protocols to ensure optimal patient and INR monitoring to facilitate earlier identification and management of out-of-range INR results. Strategies to consider include protocolization of frequency of INR testing, use of consistent testing method, standardized bridging or withholding of anticoagulation therapy for out-of-range TTR, and consideration of patient self-management and self-testing. In adult outpatients who had various indications for long-term VKA treatment, self-management and self-testing strategies resulted in fewer deaths and fewer thromboembolic events when compared with care by healthcare professionals, without risk of serious bleeding.²⁶ Avoidance of HRAEs in LVAD patients is of utmost importance as these events often deprive patients of improved quality of life. Better understanding of factors that contribute to fluctuations in TTR may help further development of strategies to improve anticoagulation management. More importantly, standardized and best practice management is needed for the VAD community as a whole.

Table 7. Percentage TTR or Sub or Supratherapeutic INR Ranges Within 60 Days of HRAE

HRAE	% TTR within 60 Days of HRAE	% Time Subtherapeutic INR Within 60 Days of HRAE	% Time Supratherapeutic INR Within 60 Days of HRAE
HCVA	46.3	32.5	21.2
ICVA	62.7	20.8	16.5
Major bleed	59.0	21.1	19.9
GI Bleed	62.9	18.3	18.8
Thrombus	60.2	19.9	19.9

GI, gastrointestinal; HCVA, hemorrhagic cerebrovascular accident; HRAE, hemocompatibility-related adverse event; ICVA, ischemic cerebrovascular accident; TTR, time in therapeutic range.

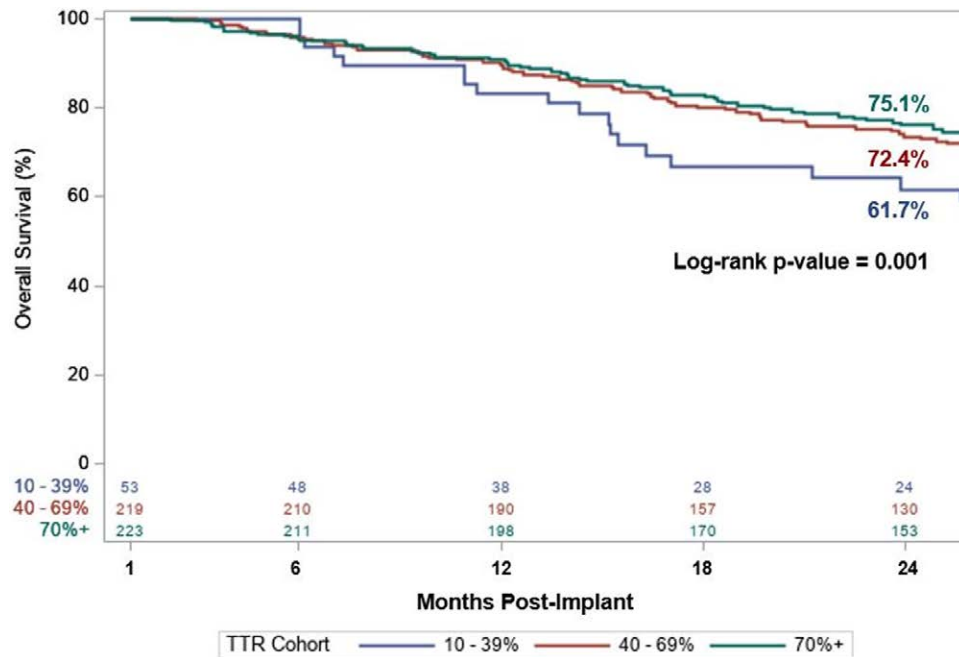


Figure 2. Kaplan–Meier Survival for low, moderate, and high TTR from 1 to 24 months postimplant. TTR, time in therapeutic range.

Limitations

This analysis is limited due to several factors. As a retrospective review of the data, this analysis is subject to selection and misclassification or information bias. A DT population alone was analyzed so results may not apply to those individuals implanted with an HVAD LVAD as a BTT strategy. Only the HVAD device, and not the control, was included in the analysis. The TTR by the Rosendaal method, although commonly used to assess effective anticoagulation strategy in cardiovascular disease populations, assumes linear variability between INR checks which can be inexact. Variability exists among center protocols for frequency of INR checks, coumadin dose management, bridging or withholding strategies for anticoagulation, and aspirin/antiplatelet usage. Variability also exists regarding healthcare provider (nurse, advanced practice provider, physician, or pharmacist) managed INR protocols. Statistical methods comparing testing methods or testing type were not evaluated. INR values were recorded but variability may have been present in testing methods such as phlebotomy laboratory draw compared with POC testing. This was not clearly identifiable from data collection. Finally, it is important to understand that although an association was identified with an increase in adverse events and low TTR, it remains unclear as to whether the higher morbidity is the cause of the low TTR versus the effect of the low TTR.

Conclusion

Achieving a higher percentage of time within a therapeutic range of goal INR can impact morbidity and mortality in a DT HVAD population. In this review, moderate (40–69%, mean 57.2%) and high ($\geq 70\%$, mean 81.3%) TTRs were associated with significantly improved survival compared with low ($\leq 39\%$, mean 27.4%) TTR. High TTR patients also experienced

significant reductions in adverse events, including stroke, pump thrombus, major bleeding, and right HF. Medtronic has recently announced the sale and distribution of the HVAD System. In light of the improved outcomes with high TTR in this analysis, mechanical circulatory support (MCS) centers should consider TTR monitoring as an important added metric for their anticoagulation strategies to optimize clinical outcomes in LVAD patients. Center-specific strategies that foster improved patient compliance, ease of monitoring, and patient reporting should also be considered. As an MCS community, standardized and best practice management of anticoagulation as well as further studies are needed.

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