Relationship Between Anticoagulation Intensity and Thrombotic or Bleeding Outcomes Among Outpatients With Continuous-Flow Left Ventricular Assist Devices

Michael E. Nassif, MD*; Shane J. LaRue, MD, MPH*; David S. Raymer, MD; Eric Novak, MS; Justin M. Vader, MD, MPH; Gregory A. Ewald, MD; Brian F. Gage, MD

Background—We evaluated thrombotic and bleeding outcomes in patients with continuous-flow left ventricular assist devices (CF-LVADs), stratified by anticoagulation intensity. Previous studies of outpatients with CF-LVADs have suggested that target international normalized ratio (INR) values <2.5 (range, 2–3) may be used. However, recent studies reported an increase in pump thrombosis among CF-LVADs, especially within the first 6 months of implant.

Methods and Results—We retrospectively reviewed 249 outpatients at our center who received a CF-LVAD between January 2005 and August 2013. Using Poisson models, we analyzed their 10,927 INRs to determine INR-specific rates of thrombotic (ischemic stroke and suspected pump thrombosis) and hemorrhagic (gastrointestinal bleeding and hemorrhagic stroke) events occurring outside of the hospital. In multivariate analyses, we adjusted for age, sex, atrial fibrillation, coronary disease, and LVAD type as time-dependent Cox proportional hazard models. During a mean follow-up of 17.6±13.6 months, thrombotic events occurred in 46 outpatients. The highest event rate (0.40 thrombotic events per patient-year) was in the INR range of <1.5, but INR values of 1.5 to 1.99 also had high rates (0.16 thrombotic events per patient-year). INR was inversely associated with thrombotic events (hazard ratio, 0.40; 95% confidence interval, 0.22–0.72; P=0.002). The optimal INR based on weighted mortality of thrombotic and bleeding events was 2.6.

Conclusions—INR is inversely related to thrombotic events occurring outside of the hospital among patients supported with CF-LVADs. INR values <2.0 increase the rate of thrombotic events occurring outside of the hospital among patients supported with CF-LVADs. (Circ Heart Fail. 2016;9:e002680. DOI: 10.1161/CIRCHEARTFAILURE.115.002680.)

Key Words: atrial fibrillation ■ follow-up studies ■ hemorrhage ■ international normalized ratio ■ stroke

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See Editorial by Connors
See Clinical Perspective

Over time, the question of anticoagulation in left ventricular assist device (LVAD) support has become complicated. In the HeartMate II destination therapy pivotal study, the incidence of thrombotic events (defined as confirmed pump thrombosis or ischemic stroke) was higher than the BTT trial study—16% at 1.7 years of follow-up. The pivotal study used warfarin with a goal INR between 2.0 and 3.0, in addition to aspirin. Subsequently, analysis of the HeartWare ADVANCE noted INR <2.0 as a risk factor for pump thrombosis. Finally, more recently, others have reported an increase in pump thrombosis among CF-LVADs, especially within the first 6 months of implant.

The reason for increased thrombosis is not clear but is likely multifactorial, with gastrointestinal bleeding (GIB), infection, varying anticoagulation bridging strategies, and suboptimal INRs potentially contributing. In addition, patient selection has changed since Food and Drug Administration
approval for destination therapy in January 2010, allowing more implants in patients potentially at higher risk of thrombosis. The objective of this study was to examine the association between INR and both thrombotic and hemorrhagic events among outpatients supported with CF-LVADs.

Methods

Study Population

We retrospectively identified patients who underwent implantation of a HeartMate II (Thoratec Corp, Pleasanton, CA) or HVAD (HeartWare Corp, Framingham, MA) between January 2005 and August 2013 at our center. Inclusion criteria for the present study were CF-LVAD placement, age ≥18 years, survived to discharge, and followed up at our institution. Exclusion criteria included patients who underwent repeat LVAD implantation (ie, pump exchange) or patients who had a hemorrhagic or thrombotic event before discharge from their implant hospitalization.

Patients were censored at the time of transplantation, LVAD explant or exchange, death, or last known follow-up. To avoid confounding by indication, patients were censored at their first hemorrhagic event (intracranial hemorrhage [ICH] or GIB) or thrombotic event (suspected pump thrombosis or ischemic stroke), that is, a patient could only contribute a maximum of 1 thrombotic event or 1 hemorrhagic event. Only events occurring outside of the hospital were included; if a patient had a thrombotic or hemorrhagic event while an inpatient they were censored.

Data Collection

Clinical data, including baseline characteristics, medications, blood products, and outcomes, were abstracted from the electronic medical record. The data were managed in the Research Electronic Data Capture database.9 The Institutional Review Board at Washington University in St. Louis approved the study.

Institutional protocol dictates that outpatient INRs are checked weekly when not in therapeutic range and every other week within the therapeutic range. The target therapeutic range for our patients supported with HeartMate II evolved was 2.0 to 2.5 from 2005 to 2008, 1.5 to 2.0 from 2008 to 2010, and 2.0 to 3.0 from 2010 to current. The target INR range for patients supported with HeartWare HVAD was 2.0 to 3.0 throughout.

We used the INR at the time of the adverse event. In patients treated with vitamin K, fresh frozen plasma, or blood transfusion before measuring the INR, we used the INR before treatment. In patients admitted with a pump thrombosis, we used the last available outpatient INR (because pump thrombosis often starts with a subclinical phase and can elevate the INR).

Definitions and Outcomes

Suspected pump thrombosis was defined as observation of obstructive thrombus in the pump or conduit post pump exchange or severe hemolysis. Severe hemolysis was defined as lactate dehydrogenase level >1000 mg/dL (4× the upper limit of normal for our laboratory) or plasma-free hemoglobin level >40 mg/dL with symptoms of decompensated heart failure in the absence of a kinked inflow or outflow cannula. An lactate dehydrogenase value >3.5× the upper limit of normal has excellent specificity and sensitivity for the diagnosis of pump thrombosis.10

GIB was defined as clinically evident or occult GIB prompting hospital admission and endoscopic evaluation. Severe anemia requiring blood transfusion in the absence of hemolysis and a bleeding source was classified as occult bleeding.

Stroke was identified as an acute neurological deficit persisting for >24 hours. A stroke was classified as hemorrhagic or ischemic based on head computed tomography. If the head computed tomography was read as ischemic stroke with hemorrhagic conversion or both ischemic and hemorrhagic strokes, then the stroke was classified as ischemic.

Weights of Thrombotic and Bleeding Events

To balance the benefits and risks of more intensive anticoagulation, events were weighted based on their expected 30-day mortality rates. Mortality rates were calculated from the onset of adverse event by averaging internal data on 455 patients with CF-LVAD (Appendix 1 in the Data Supplement) with published mortality data of ischemic stroke,11,12 ICH,13,14 GIB,15-16 and pump thrombosis.5,17 The baseline mortality rate in our LVAD population (n=455) was 0.036 deaths per month. To this baseline mortality, we added the incremental mortality rate (per month) from an adverse event (Appendix 1 in the Data Supplement): pump thrombosis, 0.16; GIB, 0.01; ischemic stroke, 0.11; and ICH, 0.49. Of note, the mortality rate after LVAD-related GI bleeding varied from 0 to 0.02 deaths per patient-month.

Statistical Analysis

When calculating event rates, the numerator was the number of adverse events. The denominator was days in each INR range as calculated according to the method described by Rosendaal et al18 for linear interpolation. The rate for each INR category was calculated using Poisson regression via generalized estimating equations to account for correlated data (Appendix 1 in the Data Supplement).

The optimal INR was determined by combining exponential models created for thrombosis and for bleeding rates. Rates for each INR category were log-transformed, and the mean INR value within each range was used as the independent variable to develop the 2 exponential models. To prevent taking the logarithm of 0, the constant 0.1 was added to each thrombosis rate. (An advantage of this approach is that it avoids relying on the Yates correction for continuity, which is conservative for 2-sided tests with rare events).19 When developing the exponential models, INR ranges were weighted by the frequency of observations.

The sum of the exponential bleeding and thrombosis models was obtained by weighting each based on mortality-associated event rates obtained independently (as detailed above). This weighted U-shaped curve was then used to determine the optimal INR value that minimized mortality.

The association between INR and clinical events was further quantified in a multivariable analysis that used Cox regression. Time to event was left truncated to account for time 0 being implant date but hazard time not beginning until discharge. Individuals were part of the at-risk group once their first INR was measured. INR was allowed to vary over time to account for repeated measurements taken during follow-up. Separate Cox models were created for both event types (bleeding and thrombosis). Cox models adjusted for age, sex, LVAD type (HeartMate II or HeartWare), history of atrial fibrillation, and history of coronary artery disease as these covariates influence bleeding or thrombotic events.5,11,15,20

In addition, the interaction of INR and time was investigated to determine if the association between INR and clinical event changed over time. Time was categorized into hospital discharge to 3 months, 3 to 6 months, and >6 months based on when INR was obtained from time of implant.

Significance was identified as a 2-sided α of <0.05. Analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Results

Patient Population

A total of 305 patients received a CF-LVAD from January 2005 until August 2013 and were discharged alive. Fifty-six patients were excluded from analysis: 20 were LVAD exchanges, 11 had thrombotic events during their index stay, 4 were followed up at other institutions, and 21 had incomplete data because of censoring before ≥2 consecutive outpatient INRs were obtained. The analysis cohort consisted of 249 patients.
The 249 patients analyzed had a median outpatient follow-up of 17.6±13.6 months with 10927 INR measurements available, an average of 1 INR every 11.8 days. Most patients were men (81%), classified as Interagency Registry for Mechanically Assisted Circulatory Support profile 2, and bridge-to-transplant approach was used for 69% of the patients (Table 1). Nearly all patients were discharged on warfarin and aspirin (96%), with 45% of patients being on 325 mg of aspirin and 51% on 81 mg of aspirin. The mean INR at discharge after LVAD implant was 2.18±0.62, and during outpatient follow-up, the mean INR was 2.16±0.77 (Figure 1).

Thrombotic Events
A total of 46 thrombotic events occurred: 32 suspected pump thrombosis and 14 ischemic strokes. The highest event rate (0.40 events per patient-year) occurred in the INR range of <1.5, but INR values of 1.5 to 1.99 also had high rates (0.16 thrombotic events per patient-year). Among the INRs >2.5 categories, there was no episode of ischemic stroke and only 1 thrombotic event per patient-year). Comparing the HR of thrombotic event by time period, there was a trend toward increased thrombotic events (HR, 1.44; \( P =0.021 \)) and trended toward significance (0.75 versus 0.25; \( P =0.05 \)).

Hemorrhagic Events
A total of 62 hemorrhagic end points occurred: 53 GI bleeds and 9 ICHs. The highest bleeding event rate (1.4 events per patient-year) occurred in the INR range >3.5 and the lowest event rates (≤0.1 events per patient-year) were in with the lowest INR categories (Figure 2A). There were 7 episodes of ICH in those with INR >2.5 and only 2 episodes of ICH with INR <2.5.

In univariate analysis, INR was inversely associated with hemorrhage (HR, 1.63; 95% CI, 1.41–1.88; \( P <0.001 \); Table 2). In a Cox proportional hazard models adjusting for age, sex, atrial fibrillation, coronary disease, and LVAD type, INR remained inversely associated with hemorrhotic events (HR, 0.40; 95% CI, 0.22–0.72; \( P =0.002 \); Table 3). The inverse association between INR and thrombotic events was statistically significant for the 3- to 6-month and >6-month postimplant timeframe but was not significant before 3 months (HR, 0.75; 95% CI, 0.34–1.65; \( P =0.47 \); Table 2). The lack of significance between INR and thrombotic events before 3 months was in spite of this period being the time of the highest incidence rate of pump thrombosis (0.37 events per patient-year). Comparing the HR of thrombotic event by INR before 3 months to after 3 months bordered on statistical significance (0.75 versus 0.25; \( P =0.05 \)).

Table 1. Baseline Characteristics of Entire Cohort

<table>
<thead>
<tr>
<th>n=249</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>55.5 (18.12–78.8)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>195 (78)</td>
</tr>
<tr>
<td>White, n (%)</td>
<td>190 (76)</td>
</tr>
<tr>
<td>BMI, mean (range), kg/m²</td>
<td>28.5 (17.3–49)</td>
</tr>
<tr>
<td>LOS implant to discharge, d</td>
<td>21.5±16.5</td>
</tr>
</tbody>
</table>

Medical history

| Atrial fibrillation, n (%) | 105 (42) |
| Current smoker, n (%) | 27 (11) |
| CAD, n (%) | 123 (49) |
| DM, n (%) | 107 (43) |
| INTERMACS profile median (IQR) | 2.0 (1.0–2.0) |
| Intracardiac thrombus, n (%) | 28 (11) |
| Bridge to transplant, n (%) | 173 (69) |

Laboratories on discharge

| AST | 51.3±41.6 |
| Hgb, g/dL | 9.58±1.34 |
| INR | 2.18±0.62 |
| PLT | 331±131 |
| Aspirin on discharge, n (%) | 244 (98) |
| Aspirin dose | 325 mg daily, n (%) | 112 (45) |
| 81 mg daily, n (%) | 137 (55) |
| Warfarin on discharge, n (%) | 240 (96) |

Values are shown as absolute numbers (percentages), mean±SD, or median (IQR). AST indicates aspartate aminotransferase; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; Hgb, hemoglobin; LOS, length of stay; INR, international normalized ratio; IQR, interquartile range; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; and PLT, platelets.
Optimal INR Range
The optimal INR was determined to be 2.6, with low rates of adverse events falling between INR values of 2.0 to 3.2. A model with no weighting (equal mortality weights for all events) favored an INR of 2.4. (Figure 3). Sensitivity analyses were performed by varying the weights of events over their plausible ranges, with minor effect on the optimal INR of 2.6 (Figure III in Appendix I in the Data Supplement).

Discussion
Anticoagulation management of outpatients with CF-LVADs remains a delicate balance between avoiding hemorrhagic and thrombotic complications. Previous studies suggested that low rates of thrombotic events may allow for lower INRs for those at high risk of bleeding,4,5 but reports of higher rates of thrombosis have cast doubt on this assertion.7,8 Here, we characterized the relationship between outpatient management of anticoagulation and both thrombotic and hemorrhagic events occurring outside of the hospital.

By analyzing ≈11,000 outpatient INRs among 249 outpatients, we demonstrated that thrombotic outcomes (suspected pump thrombosis and ischemic stroke) were the highest among the lowest INRs (<1.5), but INR values of 1.5 to 1.99 also had high rates (0.16 thrombotic events per patient-year). Although the finding that lower INR was associated with thrombosis was hypothesized, the observed time-sensitive relationship between INR and thrombosis was unexpected. This lack of a statistically significant association between INR and thrombotic events in the 0- to 3-month timeframe suggests that early pump thrombosis may be affected by INR-independent events during the index hospitalization, such as operative or device characteristics and intensity of postoperative bridging anticoagulation. Conversely, after the early postsurgical period, anticoagulation intensity predicts pump thrombosis.

An optimal INR based on weighted mortality of bleeding and thrombotic events was 2.6. In the future, it might be interesting to develop patient-specific anticoagulation strategies based on risk models that stratify a patient’s propensity to have hemorrhagic and thrombotic complications.

Our conclusions differ from an analysis of from the HeartMate II pivotal trial. That study did not find a statistical association between lower INR and thrombotic events, but there were no ischemic strokes when the INR exceeded 2.0.4 The different conclusions between studies may have been driven by the greater rate of suspected pump thrombosis that we observed (12.9% of patients for a mean follow-up of 17.6 months). Our rate was higher because we included persistent hemolysis in our definition of suspected pump thrombosis. In contrast, the HeartMate II pivotal trial captured only a thrombus in the device or its conduits. Our event rate is commensurate to what Starling et al7,21 reported (eg, 12.3% at 1 year of follow-up). Our study had high precision because we included...
Deficiency contributes to GI bleeding.23 Other LV AD studies have found that acquired von Willebrand type, were not analyzed.24 Some putative risks for thrombosis, such as non–type O blood type, were not analyzed.24 Although we did not quantify von Willebrand factor or platelet function, other LVAD studies have found that acquired von Willebrand deficiency contributes to GI bleeding.23

Furthermore, screening for thrombosis has intensified, potentially resulting in more frequent detection of suspected pump thrombosis. Similarly, given our modest sample size, some putative risks for thrombosis, such as non–type O blood type, were not analyzed.24 Finally, our event weighting may not be optimal because it was based on local mortality rates. There is almost no literature describing provider or patient weighting of LVAD-associated adverse events. Given that pump thrombosis is associated with >50% 1-year mortality or major surgery with high morbidity, we chose to weigh it slightly greater than stroke. Literature in non-VAD supported patients has assigned GI bleeding weights between 0 and 0.6.25 Modeling of optimal INR with a priori patient- or provider-derived weights for different events may a reasonable framework for prospective analyses of anticoagulation management.

In conclusion, INR and hemorrhagic events were highly correlated and INR and thrombotic events were inversely correlated. By considering both bleeding and thrombotic events, an optimal INR was determined to be 2.6, with low rates of adverse events falling between INR values of 2.0 to 3.2.

Sources of Funding
This study was supported, in part, by research funds from the National Institutes of Health (NIH grant U10 HL110309, Heart Failure Network; NIH grant T32HL110837) and grant number UL1 TR000448 R01 HL097036.

Disclosures
Dr Ewald received consulting fees from Thoratec. The other authors report no conflicts. The content is solely the responsibility of the authors.

References

Table 4. Hazard Ratio for Bleeding Events as a Function of International Normalized Ratio

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>INR</td>
<td>1.63</td>
<td>(1.41–1.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>INR, discharge - 3 mo interaction</td>
<td>2.33</td>
<td>(1.70–3.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>INR, 3- to 6-mo interaction</td>
<td>1.43†</td>
<td>(1.10–1.87)</td>
<td>0.007</td>
</tr>
<tr>
<td>INR, &gt;6 mo interaction</td>
<td>1.60†</td>
<td>(1.26–2.02)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HR shown per 1-U increase in INR. CI indicates confidence interval; HR, hazard ratio; and INR, international normalized ratio.

†P=0.021 when compared with INR ≤3 mo.
†P<0.06 when compared with INR ≤3 mo.

11,000 INR values for a mean follow-up of 17.6 months, whereas the HeartMate II pivotal trial evaluated 1294 INR values for 6 months of follow-up.

When interpreting the results of our study, several limitations must be considered. The study is retrospective and nonrandomized. To reduce confounding by indication, we censored patients at the time of their first event. However, patients at higher risk of thrombotic events may have been assigned higher INR goals from the outset. Censoring patients after their first event and excluding events occurring in the hospital both lead to underestimation of overall event rates. There are inherent limitations to the timing of INR measures and clinical events. For example, it is possible that our associations with INR and hemorrhagic events are overestimated because of the presence of a consumptive coagulopathy. In terms of secular trends in anticoagulation management, the rate of pump thrombosis has been increasing over time, and anticoagulation and antiplatelet regimens have varied over time.7,8,22 Although we did not quantify von Willebrand factor or platelet function, other LVAD studies have found that acquired von Willebrand deficiency contributes to GI bleeding.23

Finally, our event weighting may not be optimal because it was based on local mortality rates. There is almost no literature describing provider or patient weighting of LVAD-associated adverse events. Given that pump thrombosis is associated with >50% 1-year mortality or major surgery with high morbidity, we chose to weigh it slightly greater than stroke. Literature in non-VAD supported patients has assigned GI bleeding weights between 0 and 0.6.25 Modeling of optimal INR with a priori patient- or provider-derived weights for different events may a reasonable framework for prospective analyses of anticoagulation management.

In conclusion, INR and hemorrhagic events were highly correlated and INR and thrombotic events were inversely correlated. By considering both bleeding and thrombotic events, an optimal INR was determined to be 2.6, with low rates of adverse events falling between INR values of 2.0 to 3.2.

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References


**CLINICAL PERSPECTIVE**

The approach to anticoagulation after continuous-flow left ventricular assist device implantation has varied over time. Previous studies have suggested that lower international normalized ratio (INR) targets may have more acceptable risk profiles. In light of a subsequently noted increase in thrombotic complications, more aggressive anticoagulation strategies have again been adopted although evidence to support this approach is limited. We conducted a retrospective study to examine the association between INR and both thrombotic and hemorrhagic events among outpatients supported with continuous-flow left ventricular assist devices. In reviewing event rates by INR range for 249 patients, we demonstrate increased rates of thrombotic complications in ranges with an INR <2 and increased rates of hemorrhagic complications with an INR >3, providing support for the current INR goal range of 2 to 3. In addition, weighting each complication by its associated mortality provided a similar goal range, with an ideal INR of 2.6. This study is the first to provide substantive evidence supporting the current outpatient INR goal range of 2 to 3 in continuous-flow left ventricular assist device–supported patients.
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Data Supplement (unedited) at:
http://circheartfailure.ahajournals.org/content/suppl/2016/05/06/CIRCHEARTFAILURE.115.002680.DC1

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Online Supplementary Appendix

Table of Contents

Appendix S1. Additional Methodolgic details
Table S1. Weighting of adverse events
Table S2. Hemorrhagic events and event rates per total patient years in a given INR range
Table S3. Thrombotic events and event rates per total patient years in a given INR range
Table S4. Anticoagulation and Antiplatelet Protocols

Figure S1. Hemorrhagic event rates per INR range multiplied by expected 30 day mortality rates for each adverse event
Figure S2. Thrombotic event rates per INR range multiplied by expected 30 day mortality rates for each adverse event
Figure S3. Optimal INR ranges with varying weights of thrombotic and hemorrhagic events
Appendix S1 –

Event rates per patient-year were computed to account for differences in observable time among INR ranges. A Poisson model with offset equal to the log INR years, as determined by the natural log of the time spent in INR range, was used to develop estimates, confidence intervals, and compare ranges. No overdispersion was identified. Poisson models were developed using generalized estimating equations to account for correlated data corresponding to patients providing data towards multiple INR ranges.

Table S1 –

<table>
<thead>
<tr>
<th>Event</th>
<th>Internal data deaths/patient month</th>
<th>Literature Review deaths/patient month</th>
<th>Value utilized in weighing scheme</th>
</tr>
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<tbody>
<tr>
<td>Pump Thrombosis</td>
<td>0.142</td>
<td>0.18(1)</td>
<td>0.16</td>
</tr>
<tr>
<td>GI Bleed</td>
<td>0.008</td>
<td>0.01 (9)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>0.113</td>
<td>0.10 (4,5)</td>
<td>0.11</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>0.58</td>
<td>0.40 (6)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

GI = gastrointestinal

Table S2 –

<table>
<thead>
<tr>
<th>INR range</th>
<th>Patient years</th>
<th>Events Per INR range</th>
<th>Event rate per 10 patient-years</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ICH</td>
<td>GIB</td>
</tr>
<tr>
<td>0 – 1.49</td>
<td>40.32</td>
<td>0</td>
<td>3</td>
</tr>
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<td>1.50 – 1.99</td>
<td>110.74</td>
<td>1</td>
<td>10</td>
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<tr>
<td>2.00 – 2.49</td>
<td>101.26</td>
<td>1</td>
<td>20</td>
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<td>2.50 – 2.99</td>
<td>47.53</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>3.00 – 3.49</td>
<td>15.04</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>≥ 3.5</td>
<td>9.86</td>
<td>3</td>
<td>11</td>
</tr>
</tbody>
</table>

ICH = intracranial hemorrhage; GIB = gastrointestinal bleeding.
### Table S3 –

<table>
<thead>
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<th>INR range</th>
<th>Patient years</th>
<th>Event Per INR range</th>
<th>Event rate per 10 patient-years</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PT</td>
<td>Isc St</td>
</tr>
<tr>
<td>0 – 1.49</td>
<td>40.31</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>1.50 – 1.99</td>
<td>111.39</td>
<td>13</td>
<td>4</td>
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<td>2.00 – 2.49</td>
<td>101.76</td>
<td>9</td>
<td>3</td>
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<tr>
<td>2.50 – 2.99</td>
<td>47.80</td>
<td>0</td>
<td>0</td>
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<tr>
<td>3.00 – 3.49</td>
<td>15.22</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>≥ 3.5</td>
<td>9.95</td>
<td>0</td>
<td>0</td>
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</table>

PT = pump thrombosis; Isc St = ischemic stroke.

### Table S4 - Anticoagulation and Antiplatelet Protocols

<table>
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<th>2004 through 2008</th>
<th>2009 through 2011</th>
<th>2012 through Current</th>
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<tr>
<td>Intravenous anticoagulation – bridge to warfarin</td>
<td>Yes</td>
<td>Occasional</td>
<td>Yes</td>
</tr>
<tr>
<td>INR goal</td>
<td>2.0-2.5</td>
<td>1.5-2.0</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Aspirin dose (mg)</td>
<td>81 or 325</td>
<td>81 or 325</td>
<td>325</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Yes</td>
<td>Yes</td>
<td>Selective (HIT)</td>
</tr>
</tbody>
</table>

INR = international normalized ratio; HIT = heparin induced thrombocytopenia
Hemorrhagic event rates per INR range multiplied by expected 30 day mortality rates for each adverse event
Figure S2 –

Thrombotic event rates per INR range multiplied by expected 30 day mortality rates for each adverse event.
**Figure S3**

- **Gastrointestinal Bleeding**: 0.05 - 0.005
- **Intracranial Hemorrhage**: 0.60 - 0.40
- **Pump Thrombosis**: 0.10 - 0.22
- **Ischemic Stroke**: 0.08 - 0.16

Optimal INR ranges with varying weights of thrombotic and hemorrhagic events.