Antiplatelet Therapy and Adverse Hematologic Events During Heart Mate II Support

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Background—Hematologic adverse events are common during continuous flow left ventricular assist device support; yet, their relation to antiplatelet therapy, including aspirin (ASA) dosing, is uncertain.

Methods and Results—A single-center retrospective review of all patients supported by a continuous flow left ventricular assist device (Heart Mate II) from June 2006 to November 2014 was conducted. Patients were categorized into 3 groups: (1) ASA 81 mg+dipyridamole 75 mg daily (n=26) with a target international normalized ratio (INR) of 2 to 3 from June 2006 to August 2009; (2) ASA 81 mg daily (n=18) from September 2009 to August 2011 with a target INR of 1.5 to 2; and (3) ASA 325 mg daily from September 2011 to November 2014 with a target INR of 2 to 3 (n=70). Hemorrhagic and thrombotic outcomes were retrieved ≤365 days after implantation. Cumulative survival free from adverse events was calculated using Kaplan–Meier curves and Cox proportional hazard ratios were generated. Hemorrhagic events occurred in 6 patients on ASA 81 mg+dipyridamole (26%; 0.42 events per patient year; mean INR at event, 2.2), 4 patients on ASA 81 mg (22%; 0.38 events per patient year; mean INR at event, 2.0), and in 38 patients on ASA 325 mg (54%; 1.4 events per patient year; mean INR at event, 2.2); P=0.004. Patients on ASA 325 mg had a higher adjusted hazard ratio of 2.9 (95% confidence interval, 1.2–7.0 versus ASA 81 mg+dipyridamole; P=0.02) and 3.4 (95% confidence interval, 1.2–9.5 versus ASA 81 mg; P=0.02) for hemorrhagic events. Thrombotic events rates were not different between groups.

Conclusions—High-dose ASA in Heart Mate II patients treated concomitantly with warfarin is associated with an increased hazard of bleeding but does not reduce thrombotic events. (Circ Heart Fail. 2016;9:e002296. DOI: 10.1161/CIRCHEARTFAILURE.115.002296.)

Key Words: aspirin ■ hemorrhage ■ international normalized ratio ■ intracranial hemorrhage ■ thrombus

During the past 15 years, advancement and wider implementation of continuous flow left ventricular assist devices (CF LVADs) have led to marked improvement in the survival of patients with end-stage heart failure. Despite such progress, hematologic complications are common during CF LVAD support and create substantial morbidity. Major hemorrhagic adverse events (AEs) include gastrointestinal bleeding (GIB; 0.23–0.45 events per patient year [eppy]) and intracranial hemorrhage (ICH; 0.03–0.09 eppy), which are countered by thrombotic complications, such as ischemic stroke (0.05–0.11 eppy) and pump thrombosis (0.02–0.04 eppy).1,4

See Clinical Perspective
Antithrombotic strategies, including antiplatelet medications and vitamin K antagonists, are commonly prescribed during CF LVAD support, but there are limited outcome data to guide a specific regimen. The International Society of Heart and Lung Transplantation guidelines for mechanical circulatory support provide device-specific international normalized ratio (INR) goals, but the optimal dose for aspirin (ASA) remains broad at 81 to 325 mg daily and uncertain.4

LVAD implantation creates platelet dysfunction and acquired loss of high–molecular weight von Willebrand multimers, which in combination with high-dose antiplatelet therapy may lead to greater hemorrhagic AEs without a reduction in thrombosis.6,7 Therefore, in this study, we aim to examine the association of hemorrhagic and thrombotic event rates with distinct and a priori antiplatelet and anticoagulation regimens.

Methods

Study Population
We retrospectively reviewed all patients undergoing CF LVAD placement from June 1, 2006, to November 30, 2014, at Montefiore Medical Center. Only patients with the Heart Mate (HM) II device were included. Patients with perioperative AEs ≤14 days after HM II placement were excluded. Patients receiving antiplatelet therapy
Clinical Data Collection
Preoperative clinical information and baseline demographics were collected from medical charts. Patients were categorized into 3 groups based on the different antiplatelet and antithrombotic regimens prescribed a priori across 3 consecutive time periods: (1) ASA 81 mg+DPE 75 mg daily (n=26) with a target INR of 2 to 3 from June 2006 to August 2009; (2) ASA 81 mg daily (n=18) from September 2009 to August 2011 with a target INR of 1.5 to 2; and (3) ASA 325 mg daily from September 2011 to November 2014 with a target INR of 2 to 3 (n=70). DPE was discontinued after August 2009 as dual antiplatelet therapy was felt to be unnecessary because of a high incidence of GIB. In September 2011, our institution switched to high-dose ASA for all CF LVADs after we observed several thrombotic events in patients supported by the HeartWare Ventricular Assist Device.

Initial hemorrhagic (gastrointestinal, intracranial, and epistaxis) and thrombotic (ischemic stroke and pump thrombosis) outcomes were retrieved for ≤365 days of CF LVAD support. INR was retrieved for the duration of CF LVAD support and at the time of adverse hematologic events.

Definition of AEs
GIB was defined by requiring a blood transfusion and a drop in hemoglobin of ≥2 g/dL. Epistaxis was defined by warranting an inpatient admission and a blood transfusion. ICH was confirmed on head computed tomographic scan and accompanied by neurological symptoms. Ischemic cerebrovascular accident (CVA) was defined by the presence of an acute cerebral infarction noted on a head computed tomographic scan and accompanied by neurological symptoms. Device thrombosis was confirmed by the presence of thrombus within the LVAD leading to device malfunction and explantation. All device thromboses were subsequently confirmed by direct inspection of the pump.

Data Analysis
The primary end point was freedom from any hemorrhagic event. Secondary end points were freedom from GIB, epistaxis, ICH, any thrombotic event, ischemic CVA, and pump thrombosis. If patients had >1 AE, the time to each AE was used. Event rates are based on initial hematologic events. Subsequent events were excluded because those may have occurred during altered antithrombotic regimens.

Statistical Analysis
Data are displayed as mean±SD, unless otherwise specified. Baseline demographics were compared between patients in all 3 antiplatelet groups by ANOVA for continuous variables and the χ² test for categorical variables. INR during LVAD support was compared across groups by applying a mixed linear effects model. Cumulative survival free from primary and secondary end points was shown using Kaplan–Meier curves. Hazard ratios were calculated by univariable (unadjusted) and multivariable (adjusted) Cox proportional analyses. Multivariable analysis was done for all hemorrhagic events with adjustment for variables that have been shown to be associated with bleeding events in previous investigations, including age, cause of cardiomyopathy, and hypertension. Adjustment was also done for proton pump inhibitor use. The P values of ≤0.05 were considered statistically significant. Statistical analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC).

Results
Patient Characteristics
The study group comprised of 114 patients who were supported by a HM II and met the inclusion criteria. The mean age was 55±13 years, and 24% of the patients were women. Hypertension (49%), diabetes mellitus (49%), and atrial fibrillation (51%) were present in half of the patients. Table 1 shows the remaining preoperative baseline demographics and clinical information amongst patients on the 3 antiplatelet regimens. Proton pump inhibitor use after CF placement was less prevalent in patients on ASA 81 mg. INR during the entire HM II support period was similar across all 3 groups; P=0.787 (Figure 1 in the Data Supplement). Of note, INR at the time of AEs was similar between groups (Table 2). Patients receiving ASA 81 mg+DPE had a higher LVAD rotor speed in comparison with those on ASA 81 mg and ASA 325 mg.

Prevalence and Rates of Hematologic AEs
Overall, 48 (42%) patients had a hemorrhagic event and 9 (8%) had a thrombotic event during a period of 238±129 days.
Thirty-four (30%) patients had a GIB, 9 (8%) had epistaxis, and 6 (5%) patients experienced an ICH. Six (5%) patients were diagnosed with an ischemic CVA, and 4 (4%) had pump thrombosis.

Table 2 compares AEs that occurred between groups. Proportionally, more patients on ASA 325 mg (54%; 1.38 eppy) had a hemorrhagic event in comparison with those on ASA 81 mg+DPE (26%; 0.42 eppy) and ASA 81 mg (22%; 0.38 eppy). Similarly, more GIB occurred in patients on ASA 325 mg (37%; 0.80 eppy) in comparison with those on ASA 81 mg+DPE (19%; 0.33 eppy) and ASA 81 mg (17%; 0.26 eppy). A higher percentage of patients on ASA 325 mg had epistaxis (11%; 0.21 eppy) and ICH (7%; 0.12 eppy) than on ASA 81 mg+DPE (no epistaxis; ICH: 4%; 0.06 eppy) or ASA 81 mg (epistaxis: 6%; 0.09 eppy; no ICH).

Thrombotic events occurred in a greater proportion of patients on ASA 325 mg (10%; 0.17 eppy) in comparison with those on ASA 81 mg+DPE (4%; 0.06 eppy) and ASA 81 mg (6%; 0.08 eppy), but this difference did not reach statistical significance. Ischemic CVA occurred in similar rates on ASA 325 mg (6%; 0.10 eppy) in comparison with ASA 81 mg+DPE (4%; 0.06 eppy) and ASA 81 mg (6%; 0.08 eppy). Only patients on ASA 325 mg had pump thrombosis (6%; 0.09 eppy).

**Likelihood of Hemorrhagic and Thrombotic Events**

At the end of the follow-up period, survival free from hemorrhagic events was significantly lower in patients on ASA 325 mg (46%) in comparison with ASA 81 mg+DPE (74%) and ASA 81 mg (78%; $P=0.004$ (Figure 1A). Patients on ASA 325 mg had a higher adjusted hazard ratio of 2.86 (95% confidence interval, 1.2–7.0 versus ASA 81 mg+DPE; $P=0.02$) and 3.40 (95% confidence interval, 1.2–9.5; versus ASA 81 mg; $P=0.02$) and for hemorrhagic events (Table 3). In univariable analysis, there was no statistically significant difference in thrombotic events between patients on ASA 325 mg in comparison with ASA 81 mg+DPE (2.6 [95% confidence interval, 0.32–21]; $P=0.37$) and ASA 81 mg (1.9 [95% confidence interval, 0.2–15.7]; $P=0.54$).

**Cause of GIB**

As stated above, GIB occurred more often in patients on ASA 325 mg in comparison with the other 2 groups. Arteriovenous malformations were found in a similar proportion of patients with GIB on ASA 81 mg+DPE (1; 33%), ASA 81 mg (2; 40%), and ASA 325 mg (10; 38%). Non–arteriovenous malformation causes were similar across groups (Figure 2).

**Discussion**

The principal findings of this investigation demonstrate that during HM II support, patients on ASA 325 mg have a 3-fold increased hazard of hemorrhagic events in comparison with those on ASA 81 mg+DPE or ASA 81 mg alone. This augmented probability of hemorrhagic events was not offset by a reduction in thrombotic events with high-dose ASA. These findings are not likely to be confounded by a variation in

<table>
<thead>
<tr>
<th>Event, n (%), eppy</th>
<th>ASA 81 mg+DPE, n=26</th>
<th>INR</th>
<th>ASA 81 mg, n=18</th>
<th>INR</th>
<th>ASA 325 mg, n=70</th>
<th>INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhagic event</td>
<td>6 (26); 0.42</td>
<td>2.2±0.8</td>
<td>4 (22); 0.38</td>
<td>2.0±0.7</td>
<td>38 (54); 1.38</td>
<td>2.2±0.8</td>
</tr>
<tr>
<td>GIB</td>
<td>5 (19); 0.33</td>
<td>2.2±0.8</td>
<td>3 (17); 0.26</td>
<td>2.0±0.7</td>
<td>26 (37); 0.80</td>
<td>2.2±0.8</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>0, 0</td>
<td>*</td>
<td>1 (6); 0.09</td>
<td>1.9</td>
<td>8 (11); 0.21</td>
<td>2.1±0.6</td>
</tr>
<tr>
<td>ICH</td>
<td>1 (4); 0.06</td>
<td>2.1</td>
<td>0; 0</td>
<td>*</td>
<td>5 (7); 0.12</td>
<td>1.9±0.4</td>
</tr>
<tr>
<td>Thrombotic event</td>
<td>1 (4); 0.06</td>
<td>1.7</td>
<td>1 (6); 0.08</td>
<td>2.1</td>
<td>7 (10); 0.17</td>
<td>2.0±0.6</td>
</tr>
<tr>
<td>Ischemic CVA</td>
<td>1 (4); 0.06</td>
<td>1.7</td>
<td>1 (6); 0.08</td>
<td>2.1</td>
<td>4 (6); 0.10</td>
<td>2.0±0.3</td>
</tr>
<tr>
<td>Pump thrombosis</td>
<td>0, 0</td>
<td>*</td>
<td>0; 0</td>
<td>*</td>
<td>4 (6); 0.09</td>
<td>2.0±0.9</td>
</tr>
</tbody>
</table>

ASA indicates aspirin; CVA, cerebrovascular accident; DPE, dipyridamole; eppy, events per patient year on left ventricular assist device support; GIB, gastrointestinal bleeding; ICH, intracranial hemorrhage; and INR, international normalized ratio.

No events.

Figure 1. Kaplan–Meier curves showing the survival free from hemorrhagic and thrombotic events. ASA indicates aspirin.
of ASA on GIB has been previously shown in large non-LV AD population studies, such as the Nurses' Health Study. The protective effect of low-dose ASA is not related to alterations in the cause of GIB. Similar to GIB, there was a 2- to 3-fold rise in the rates of epistaxis (0.21 eppy) and ICH (0.12 eppy) with high-dose ASA in comparison with ASA 81 mg+DPE (no epistaxis; ICH: 0.06 eppy) and ASA 81 mg (epistaxis: 0.09; no ICH). ICH was the most devastating AE as it led to death in all 5 patients inflicted with it on high-dose ASA. Although the elevated hazard ratio for ICH with high-dose ASA did not reach statistical significance, further analysis of a larger series of patients is needed to evaluate the risk with ASA dosing. In this context, it is noteworthy that high-dose ASA is recommended in the HeartWare Ventricular Assist Device continued access protocol despite a relatively high rate of ICH in the initial experience.

The major impetus for high-dose antiplatelet ASA therapy is to prevent thromboembolic events. However, in this analysis, the observed rates of thrombotic events with ASA 325 mg were similar to those seen with ASA 81 mg+DPE and ASA 81 mg. Our findings are similar to another investigation conducted with the HM II device in which patients off ASA therapy showed no change in thromboembolic events. Moreover, preliminary results of the European cohort of the Study of Reduced Anti-coagulation/Anti-platelet Therapy in Patients With the HeartMate II Left Ventricular Assist System (TRACE) study indicate that an a priori antiplatelet therapy free regimen may reduce GIB rates without increasing thromboembolic event rates in HM II patients. The final analyses of this multicenter trial may shed further light on the effect of reduced antiplatelet therapy on AEs.

No pump thrombosis occurred on ASA 81 mg+DPE or ASA 81 mg alone, that were administered from September 2006 to August 2011. However, 4 pump thrombosis occurred in 70 patients on ASA 325 mg during September 2009 to November 2014, leading to an event rate of 0.09 per patient year. This rate of pump thrombosis in the most recent period occurred despite high-dose ASA and is consistent with recent multicenter reports of increasing pump thrombosis rates in LVADs, possibly suggesting that antiplatelet therapy has little effect on thrombosis rates.

There are multiple limitations to the current investigation that need to be mentioned. Foremost, this study is limited by a retrospective design that can lead to information bias, which may arise if not all AEs were appropriately documented correctly in medical charts. To ensure accuracy, we verified all AEs by cross referencing them with concurrent laboratory, radiological, and endoscopic studies. Because different antiplatelet regimens spanned various time periods, reported outcomes could be confounded by alterations in CF LVAD management strategy, such as changing INR targets and variation in rotor speed. Because of the relatively low number of AEs and to maintain the validity of the multivariable model, adjustment was not feasible for all covariables that may potentially affect AEs. Reported findings are limited by a small sample size in each group and need to be confirmed in larger multicenter populations.

In conclusion, our data show that with ongoing anticoagulation, high-dose ASA is associated with more hemorrhagic events and no reduction in thrombotic events, in comparison with low-dose ASA in patients supported by HM II. To further explore this association, randomized studies comparing antithrombotic regimens in HM II recipients are warranted.

### Table 3. Hazard Ratio Estimates for an Adverse Event

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Hemorrhagic event</th>
<th>p-value</th>
<th>Multivariable Adjusted</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA 325 mg vs ASA 81 mg+DPE</td>
<td>3.0 (1.3–7.1); 0.01</td>
<td>2.67 (1.2–7.0); 0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GIB</td>
<td>2.2 (0.86–5.8); 0.10</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>2.0 (0.2–17.2); 0.52</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombotic event</td>
<td>2.6 (0.32–21); 0.37</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic CVA</td>
<td>1.5 (0.2–13.0); 0.74</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pump thrombosis</td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASA indicates aspirin; CI, confidence interval; CVA, cerebrovascular accident; DPE, dipyridamole; and GIB, gastrointestinal bleeding.

*Hazard ratio not generated because of a limited number events.
†Adjusted for age, hypertension, cause of cardiomyopathy, and proton pump inhibitor use.

Figure 2. The cause of gastrointestinal bleeding in patients on separate antiplatelet regimens. ASA indicates aspirin; AVM, Arteriovenous malformation; and DPE, dipyridamole.
**Sources of Funding**

This study was supported by intramural research funds.

**Disclosures**

Dr Goldstein serves as a consultant for Thoratec Inc. He also serves on the scientific advisory board of HeartWare and is their surgical proctor. Dr Jorde is a medical advisory board member for Thoratec Inc and HeartWare. The other authors report no conflicts.

**References**


**CLINICAL PERSPECTIVE**

Hematologic adverse events lead to significant morbidity and mortality during left ventricular assist device support, and their association with various antiplatelet regimens is uncertain. We sought to determine the effect of 3 distinct antiplatelet and antithrombogenic regimens prescribed on an a priori basis after Heart Mate II placement. In this retrospective analysis, patients were categorized into 3 groups: (1) aspirin (ASA) 81 mg+dipyrindol 75 mg daily with a target international normalized ratio of 2 to 3 from June 2006 to August 2009; (2) ASA 81 mg daily (n=18) from September 2009 to August 2011 with a target international normalized ratio of 1.5–2; and (3) ASA 325 mg daily from September 2011 to November 2014 with a target international normalized ratio of 2 to 3 (n=70). Hemorrhagic and thrombotic outcomes were retrieved ≤365 days after Heart Mate II implantation. The actual international normalized ratio was not different across groups over the studied period. Patients on ASA 325 mg had a higher adjusted hazard ratio of 2.9 (95% CI, 1.2–7.0 versus ASA 81 mg+dipyrindol; P=0.02) and 3.4 (95% CI, 1.2–9.5 versus ASA 81 mg; P=0.02) for hemorrhagic events. Thrombotic events rates were not different between groups. These findings suggest that reduced antiplatelet regimens may lessen the burden of hemorrhagic events during Heart Mate II support.
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Supplemental figure 1: Changes in the international normalized ratio (INR) overtime across groups.