GI Bleeding in the Era of Continuous-Flow Left Ventricular Assist Devices

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Pharmacy Grand Rounds
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Objectives

• Discuss the history of left ventricular assist devices and the associated complications post-implantation

• Review the pathophysiology of gastrointestinal bleeding in patients with left ventricular assist devices

• Identify potential pharmacologic options for the treatment and prevention of gastrointestinal bleeding
Heart Failure in the United States

- 6.5 million affected and rising
  - 250,000 with end-stage heart failure
- 1 million new cases annually

Left Ventricular Assist Devices (LVADs)

1966 – First LVAD (wean to recovery)
1970 – NIH LVAD working group formed
1978 – First LVAD implanted as BTT
1984 – First Successful LVAD for BTT
1990s – Interest declined due to complications

NIH = National Institutes of Health
BTT = Bridge to Transplantation

REMATCH (2001)

Survival (probability)

LVAD

Medical therapy

p = 0.09

p = 0.09

Months

Continuous-Flow HeartMate II™

Pulsatile LVAD (2009)

Continuous LVAD (2009)

Medical therapy (2001)

Survival (probability)

Months

p = 0.008 (2009)

p = 0.09 (2001)

Trends in Heart Transplantation

- Wait List Additions
- #Transplanted
- LVAD Implants

Complications of Continuous-Flow LVADs

- Infection
- Bleeding
- Arrhythmias
- Respiratory Failure
- Right Heart Failure
- Renal Dysfunction
- Pericardial drainage
- Psychiatric episode
- Hypertension
- Venous thromboembolism
- Stroke
- Hepatic dysfunction
- Other neurologic dysfunction
- Need for device replacement

Complications of Continuous-Flow LVADs

- Infection: 50%
- Bleeding: 40%
- Arrhythmias: 30%
- Respiratory Failure: 20%

Iatrogenic Anticoagulation

Pump Thrombosis at 1 year (%)

Year of Implantation

"Clotters" vs. "Bleeders"

<table>
<thead>
<tr>
<th>Characteristic*</th>
<th>PT (n = 8)</th>
<th>No PT (n = 56)</th>
<th>p-value</th>
<th>GIB (n = 15)</th>
<th>No GIB (n = 49)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean</td>
<td>55.6</td>
<td>56.4</td>
<td>0.87</td>
<td>58.3</td>
<td>55.7</td>
<td>0.50</td>
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<tr>
<td>Female</td>
<td>4 (50)</td>
<td>9 (16)</td>
<td>0.03</td>
<td>5 (33)</td>
<td>8 (16)</td>
<td>0.15</td>
</tr>
<tr>
<td>Prior VTE</td>
<td>1 (13)</td>
<td>7 (13)</td>
<td>1.00</td>
<td>1 (7)</td>
<td>7 (14)</td>
<td>0.44</td>
</tr>
<tr>
<td>Prior GIB</td>
<td>0 (0)</td>
<td>3 (5)</td>
<td>0.50</td>
<td>0 (0)</td>
<td>3 (6)</td>
<td>0.33</td>
</tr>
<tr>
<td>INR, mean</td>
<td>2.1</td>
<td>2.24</td>
<td>0.24</td>
<td>2.21</td>
<td>2.27</td>
<td>0.67</td>
</tr>
<tr>
<td>Antiplatelet</td>
<td>1 (13)</td>
<td>28 (50)</td>
<td>0.05</td>
<td>7 (47)</td>
<td>23 (47)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

*n (%) unless otherwise noted
More at Play?

<table>
<thead>
<tr>
<th></th>
<th>LVAD (n = 159)</th>
<th>Control (n = 159)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>55±13</td>
<td>64±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>121 (76%)</td>
<td>90 (57%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>INR at GIB</td>
<td>2.3±1.3</td>
<td>3.3±2.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

GIB = GI Bleed
GIAD = GI angiodysplasia

Acquired von Willebrand Syndrome

vWF multimer deficiency → Shear stress → Proteolysis (ADAMTS13) → Impaired platelet-mediated homeostasis → vWF deformation

vWF = von Willebrand Factor

Arteriovenous Malformations

Pseudo-Heyde Syndrome
- Narrow pulse pressure
- ↑ Intraluminal pressure
- Mucosal vein dilation

BLEEDING
- vWF deficiency
- Anticoagulation
- Stress

Mayo Foundation for Medical Education and Research
Hospital Readmissions

- 115 CF-LVADs, follow-up ~1.5 years
  - 29% with 1 readmission
  - 15% with 2 readmissions
  - 29% with >2 readmissions


CF-LVAD = Continuous-flow LVAD
Morbidity and Mortality

- Deaths related to LVAD GIB are rare
- Morbidity is significant

Diagnostic Evaluation

- Clinical suspicion
- Bleeding source identified in only ~50%

Etiology

<table>
<thead>
<tr>
<th>Condition</th>
<th>% Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVM</td>
<td>30</td>
</tr>
<tr>
<td>Ulcer</td>
<td>20</td>
</tr>
<tr>
<td>Polyp</td>
<td>15</td>
</tr>
<tr>
<td>Erosion</td>
<td>10</td>
</tr>
<tr>
<td>Hemorrhoid</td>
<td>10</td>
</tr>
<tr>
<td>Diverticula</td>
<td>5</td>
</tr>
</tbody>
</table>
Treatment Approach

• Resuscitation
  • Transfusions
  • Reversal typically avoided
  • Local intervention during scoping

• Pump speed reduction

• Empiric proton pump inhibitors

• Adjustment of anticoagulation program

• Pharmacologic therapy for recurrence
Anticoagulation Program

- Patient specific
- No standardized, validated approach developed

- ↓ Anticoagulant
  - INR 2.0-3.0
  - INR 2.0-2.5
  - INR 1.8-2.2
  - d/c warfarin

- ↓ Antiplatelet
  - Aspirin 325mg
  - Aspirin 81mg
  - d/c aspirin
Danazol

• Synthetic androgen
  • Progestin-like effects
  • Inhibits IL-1 and TNF-α
  • Vascular stability

• Treatment considerations
  • Thromboembolic events
  • Hepatotoxic
  • Intracranial hypertension
  • Teratogenic

Danazol in LVADs

- 59 y/o male s/p HMII™
- 9 hospitalizations for GIB
- 40 pRBCs 7 EGDs 8 other scopes (AVMs)
- Danazol 200mg twice daily x 49 days
- No GIB x 9 months

<table>
<thead>
<tr>
<th>Study</th>
<th>Before Danazol</th>
<th>After Danazol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schettle et al. (n = 19)</td>
<td>8.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Mean pRBCs (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean hospitalizations (n)</td>
<td>3.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Falls et al. (n = 5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean time between hospitalizations (m)</td>
<td>1.5</td>
<td>4.4</td>
</tr>
</tbody>
</table>

HM = HeartMate II™
GIB = GI Bleed
pRBC = packed red cells
EGD = esophagastroduodenoscopy
AVM = ateriovenous malformation

Thalidomide

- **Mechanism**
  - Anti-angiogenic
  - Inhibits VEGF

- **Treatment considerations**
  - Prothrombotic
  - Bone marrow suppression
  - Fluid retention
  - Neuropathy
  - Teratogenic
  - Thalomid® REMS
  - Special handling

**Plasma levels of VEGF (pg/mL)**

- Pre-thalidomide: 140 pg/mL
- Post-thalidomide: 60 pg/mL

\[ p < 0.001 \]

VEGF = vascular endothelial growth factor
REMS = Risk evaluation and mitigation strategies

# Thalidomide in LVADs

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th># episodes</th>
<th>Documented AVM</th>
<th>GIB Effect</th>
<th>Other outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>4</td>
<td>Yes</td>
<td>No recurrence</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>4</td>
<td>Yes</td>
<td>No recurrence</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>62</td>
<td>4</td>
<td>Yes</td>
<td>No recurrence</td>
<td>Discontinued (AE)</td>
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<tr>
<td>4</td>
<td>63</td>
<td>2</td>
<td>Yes</td>
<td>No recurrence</td>
<td>Discontinued (AE)</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>3</td>
<td>No</td>
<td>No recurrence</td>
<td>Dose reduction (AE)</td>
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<tr>
<td>6</td>
<td>29</td>
<td>3</td>
<td>No</td>
<td>Reduced bleeding</td>
<td>Transplanted</td>
</tr>
<tr>
<td>7</td>
<td>61</td>
<td>3</td>
<td>Yes</td>
<td>No recurrence</td>
<td>Transplanted</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>2</td>
<td>Yes</td>
<td>Reduced bleeding</td>
<td>Expired</td>
</tr>
<tr>
<td>9</td>
<td>65</td>
<td>4</td>
<td>Yes</td>
<td>-</td>
<td>Expired</td>
</tr>
<tr>
<td>10</td>
<td>66</td>
<td>1</td>
<td>No</td>
<td>No recurrence</td>
<td>Discontinued (AE)*</td>
</tr>
<tr>
<td>11</td>
<td>52</td>
<td>1</td>
<td>No</td>
<td>No recurrence</td>
<td>Discontinued (AE)</td>
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<tr>
<td>12</td>
<td>67</td>
<td>1</td>
<td>No</td>
<td>No recurrence</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>55</td>
<td>3</td>
<td>No</td>
<td>No recurrence</td>
<td>-</td>
</tr>
</tbody>
</table>

*recurrent GIB after discontinuation
AVM = arteriovenous malformation
AE = adverse event

Octreotide

• Somatostatin analog
  • ↓splanchnic blood flow
  • Inhibits angiogenesis
  • Improves platelet aggregation

• Treatment considerations
  • Relatively benign
  • GI disturbances
  • Increased blood pressure
  • Impairment of glucose homeostasis
Octreotide in LVADs

Hayes et al. (2010)
- Retrospective analysis of CF-LVADs ($n = 5$ received octreotide)
- Averaged 2 prior GIB events
- Received 25mcg/min infusion, 100mcg SQ BID or 10mg IM q4weeks
- “GI bleeding was successfully treated”

Aggarwal et al. (2012)
- Retrospective analysis of CF-LVADs ($n = 13$ received octreotide)
- Dosing not reported (SQ or continuous infusions used)
- No differences noted in mortality, rebleeding, length of stay, or usage of pRBCs, FFP, Cryo, platelets

Octreotide in LVADs

Loyaga-Rendon et al. (2015)
- Case series (n = 7)
- Averaged 3 prior GIB admissions (14 pRBCs)
- Received 50mcg SQ BID or LAR 20mg IM q4weeks
- Non-significant reduction in hospitalization, pRBCs, and diagnostic procedures
- Safety: abdominal cramps, diarrhea

Malhorta et al. (2017)
- Prospective analysis (n = 10)
- Only 3 patients with prior GIB
- Received LAR 20mg IM q4weeks x 28 weeks
- No recurrent GIB at 28 weeks
- Possible VEGF benefits
- Safety: no adverse effects reported

Malhorta R et al. ASAIO J 2017;ahead of print.
Other Potential Options

- Doxycycline
- von Willebrand factor concentrate
- Hormones
- Anti-fibrinolytics
- Desmopressin
- Angiotensin II antagonizers
Clinical Vignette

- 64 y/o male with history notable for end-stage ischemic cardiomyopathy s/p HeartMate II implantation as DT 60 days prior now presents with melanotic stools, coffee ground emesis, and syncopal event this morning.

- EMS – Hemodynamically stable, Hgb 8, INR 1.8
  - Transfused 2 pRBCs
Clinical Vignette

• Admission history since LVAD implant
  • 1st admission – EGD with APC for angioectasias
  • 2nd admission – EGD with APC and clipping for AVM in the gastric antrum
    • INR goal adjusted to 2.0-2.5

• Current anticoagulation program
  • Warfarin, adjusted to INR goal 2.0-2.5
  • Aspirin 325mg daily
Question 1

• What factors are probably contributing to gastrointestinal bleeding in this patient?
  A. Older age
  B. Anticoagulation
  C. LVAD
  D. Previous GI bleeding
  E. All of the above
Diagnostic Evaluation

• Repeat blood draw reveals Hgb 9.9, INR 2.0
• Hemodynamically stable
• Interrogation of LVAD reveals normal functioning, with no power spikes
• GI bleed team consulted and patient taken to EGD suite
Question 2

• What is the likely etiology of gastrointestinal bleeding in this patient?
  A. Peptic ulcer
  B. Hemorrhoid
  C. Arteriovenous malformation
  D. Rectal ulcer
Diagnostic Evaluation

- Findings on EGD
  - Altered blood/coffee ground-like material in the gastric antrum, gastric fundus, and gastric body
  - One bleeding angioectasia found in the stomach
    - Treated with APC and clips placed
Question 3

• Based on the presentation, how would you approach the future prevention of GI bleeding in this patient?
  
  A. Discontinue warfarin
  B. Danazol 200 mg BID
  C. Octreotide LAR 20mg IM q4weeks
  D. Change warfarin to apixaban
Conclusions

• LVADs provide survival benefit but increase the risk of GI bleeding

• GI bleeding in LVADs is multifactorial and complex

• While limited prospective data exist, there are emerging therapies that have prevented GI bleeding in patients with LVADs
“If you can think of how much love there would be in hundreds of hearts, then that is how much love there is in a plastic heart”

Michael E DeBakey, MD
ca. 1966
Questions & Discussion
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