Gastrointestinal Bleeding: Diagnosis and Management Strategies

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The following relationships exist related to this presentation:

- Research Grant: Abbott
- Consultant: Abbott (no honoraria)
GIB does **NOT** kill CF-LVAD recipients
The “scope” of the problem

- Most common cause of morbidity and hospital readmission

- Incidence is ≈ 25%

- Blood product requirement (sensitization) - BTT

- Reduced QOL
Risk factors for GIB in CF-LVADs

- Older age
- Female gender
- Ischemic cardiomyopathy
- Prior h/o GIB
- Right ventricular dysfunction
- Destination therapy
- Low Pulsatility Index
- Dual-antiplatelet therapy
- Elevated INR
GI bleed in LVAD patients is more common than similarly anticoagulated controls with valvular replacement.

Schrode /Sauer  CGH 2014

GIB is greater in the era of CF-LVADs than in the era of pulsatile-flow LVADs.

CF-LVADs

Joy et al AJC 2016
Pathogenesis of GIB during CF-LVAD support

**Hematologic factors**

Antithrombotic therapy

+ ADAMTS13

+ Acquires vW deficiency:
  - all pts,
  - all CF-LVADs
  Less with:
  - Lower speed
  - HM3

**Anatomic factors**

Angiodysplasia

45-65% of GIB

- Ischemia / low pulsatility
- Inflammation
- Altered angiogenesis (angiodysplasia)
TNF-alpha is a central regulator of altered angiogenesis in CF-LVADs

1) Is Angiodyplasia a focal or diffuse GI process and 2) is it a systemic process?

Tissue Factor expression → TGF-β + HIF-1 → + TGF-β + HIF-1

Thrombin generation → Pericyte death → Decreased Ang-1 expression → Endothelial destabilization → Endothelial proliferation

1) Is Angiodyplasia a focal or diffuse GI process and 2) is it a systemic process?
Angiodysplasia is a diffuse process in the GI track of CF-LVADs

Humans
- LVAD; N=4
- Control; N=4

Cows
- LVAD; N=2
- Control; N=4

Sheeps
- LVAD; N=3
- Control; N=3

Autopsy samples mid-jejunum (not AVM sites)
Angiodysplasia is a systemic process in HF and LVAD

**1st Hit**

**2nd Hit**

Antithrombotic therapy + Acquired vW deficiency = GIB

Patel / Jorde JACC-HF 2017
What shall we do with warfarin? Try to continue
Outcomes in HeartMate II Patients With No Antiplatelet Therapy: 2-Year Results From the European TRACE Study

Ivan Netuka, MD, PhD, Pierre-Yves Litzler, MD, PhD, Michael Berchtold-Herz, MD, Ernest F. Fisher, MD, Daniel Zimpfer, MD, Laura Damme, RN, MPH, Kartik S. Sundararwaran, PhD, David J. Farrar, PhD, and Jan D. Schmitt, MD, on behalf of the EU TRACE Investigators

Department of Cardiac Surgery, Institute for Clinical and Experimental Medicine, Prague, Czech Republic; Department of Thoracic and Cardiovascular Surgery, Rossen University Hospital Charles Nicolle, Rossen, France; Department of Cardiovascular Surgery, Heart Center, University of Freiburg, Freiburg, Germany; Department of Thoracic and Cardiovascular Surgery, CHU Pitié-Salpêtrière, Paris, France; Department of Cardiothoracic Surgery, University of Vienna, Vienna, Austria; Clinical Affairs, Research and Scientific Affairs, St. Jude Medical, Inc, Pleasanton, California; Department of Cardiac Thoracic, Transplantation and Vascular Surgery, Hanover Medical School, Hanover, Germany; and Second Department of Surgery, Department of Cardiovascular Surgery, First Faculty of Medicine, Charles University in Prague, Prague, Czech Republic.

Background. Current recommendations of antithrombotic therapy for HeartMate II (HMI) patients include the use of both an anticoagulant and an antiplatelet agent. Because bleeding is still the most frequent adverse event, the TRACE (Study of Reduced Anti-Coagulation/Anti-platelet Therapy in Patients with the HeartMate II) study was initiated to evaluate the incidence of adverse events in HMII patients on reduced antithrombotic (RT) therapy.

Methods. HMII patients (n = 101) from nine centers were enrolled in the European arm of TRACE and were managed on a single anticoagulant (vitamin K antagonist) with no antiplatelet agents. An analysis of bleeding and thromboembolic adverse events from all 101 patients with 2-year follow-up after initiation of RT therapy is reported here.

Results. Median age was 56 years (range, 18 to 72 years), 93% were men, 70% had an Interagency Registry for Mechanically Assisted Circulatory Support profile 1 to 3, and 82% received the HMII as a bridge to transplantation. Ninety-two percent were placed on RT therapy as a center standard of care or due to physician preference and 6% as a response to bleeding. Median HMII support duration on RT therapy was 25 months (range, 1 to 93 months). Median international normalized ratio was 2.31 (quartile 1 to quartile 3: 2.07 to 2.60). At 2 years, freedom from bleeding, ischemic stroke, hemorrhagic stroke, and pump thrombosis after initiation of RT therapy was 81% ± 6%, 96% ± 2%, 94% ± 3%, and 94% ± 3%, respectively.

Conclusions. The 2-year analysis of the observational European TRACE study suggests that managing HMII patients with a vitamin K antagonist with a target international normalized ratio of 2.3 without antiplatelet therapy may help to reduce the incidence of major bleeding without increasing the risk of thromboembolic events, including ischemic stroke and pump thrombosis.
- Vasoconstriction
- Increase platelet function
- Decrease angiogenesis

Houston BA JHLT 2017

LVAD since 2004
<table>
<thead>
<tr>
<th>Study year (no. participants)</th>
<th>Study Design</th>
<th>Dosing Strategy</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide 2014 (n=1)</td>
<td>Case report</td>
<td>Thalidomide 50 mg twice/day</td>
<td>Resolution of upper and lower GIB</td>
<td>Patient was maintained on warfarin therapy (INR goal 1.8-2.2) during thalidomide therapy</td>
</tr>
<tr>
<td>Thalidomide 2015 (n=8)</td>
<td>Case series</td>
<td>Thalidomide 50 mg twice/day, with the dose titrated up by 50 mg every 2 wks until achieving a goal of 200 mg/day if bleeding persists</td>
<td>Seven of eight patients showed reduction or elimination of bleeding episodes</td>
<td>High rate of dose reductions or discontinuations (three of eight patients)</td>
</tr>
</tbody>
</table>

![Diagram of Vascular Endothelium (Angiogenesis)](image-url)
**GIB 1st episode**

Hold Coumadin then restart when GIB subsides INR 2.0-2.5
Stop ASA
Start/continue/increase ARBs/ACEIs (BP control)

↓

**GIB 2nd episode**

Hold Coumadin then restart when GIB subsides INR 1.8-2.2
Octreotide 100 mg SQ TID / 20 mg IM monthly

↓

**GIB 3rd episode**

Stop Coumadin
Consider Thalidomide
Attenuated pulsatility (low PI, high speed) contributes to GIB

1. Will decrease CF-LVAD speed reduce GIB? Probably (le)
2. Should we decrease the speed? **NO**
   (PREVENT recommendations speed >9000 rpm)
What are the hemocompatibility properties of all the drugs we are using in CF-LVAds?

- Sildenafil (platelet dysfunction)
- Digoxin (anti-angiogenesis / HIF-1)
- BBs (carvedilol vs. metoprolol)
- Statins (anti-angiogenesis at high dose)
- SSRIs (platelet dysfunction)

Large clinical trials MOMENTUM 3 / ENDURANCE
Multicenter RCT focusing on medical therapy
(eg PREVENT II)
The “scope” of the problem
CUMC HF/GI Team

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Tamas Gonda, MD

Jordan Axelrad, MD

Alberto Pinsino, MD
Dew Thanataveerat, MPH
Pauline Trinh, MPH

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Dr. Gonda

CT Surgery
Dr. Eisenberger

PHARMACIST
D. Jennings

Anesthesia

RENAL
Dr. Radhakrishnan

HEMATOLOGY
Dr. Willey

VAD PROGRAM MANAGER
B. Cagliostro

VAD CORE (MDs, NPs and PAs)

SOCIAL WORKER
M. Staker

PALLIATIVE CARE
Dr. Nakagawa

COLUMBIA UNIVERSITY MEDICAL CENTER

NewYork-Presbyterian
# CUMC Experience: Predictors of GIB in 428 CF-LVAD recipients

<table>
<thead>
<tr>
<th>Predictor</th>
<th>LVAD patients without GIB (n=341; 79.7%)</th>
<th>LVAD patients with GIB (n=87; 20.3%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at LVAD implantation</strong></td>
<td>55.3 +/- 13.6</td>
<td>62 +/- 11.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Etiology of HF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>116 (38.2%)</td>
<td>53 (60.9%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Nonischemic</td>
<td>188 (61.8%)</td>
<td>34 (39.1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>137 (49.7%)</td>
<td>68 (78.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Non-white</td>
<td>139 (50.4%)</td>
<td>19 (21.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Type of therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Destination therapy</td>
<td>90 (29.7%)</td>
<td>42 (48.3%)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Bridge to transplant</td>
<td>214 (70.4%)</td>
<td>45 (51.7%)</td>
<td></td>
</tr>
</tbody>
</table>

Axelrad / Yuzefpolskaya JHLT 2018
## CUMC Experience: Index GIB

<table>
<thead>
<tr>
<th></th>
<th>Total (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median days from LVAD to GIB</strong></td>
<td>55</td>
</tr>
<tr>
<td><strong>Bleeding Presentation</strong></td>
<td></td>
</tr>
<tr>
<td>UGIB (melena, hematemesis, coffee-ground emesis)</td>
<td>30 (34.5%)</td>
</tr>
<tr>
<td>LGIB (hematochezia)</td>
<td>19 (21.8%)</td>
</tr>
<tr>
<td>Occult (hemepositive stool, iron deficiency anemia)</td>
<td>38 (43.7%)</td>
</tr>
<tr>
<td><strong>Baseline medications prior to GIB</strong></td>
<td></td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>87 (100%)</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>4 (4.6%)</td>
</tr>
<tr>
<td>Aspirin 81mg</td>
<td>77 (88.5%)</td>
</tr>
<tr>
<td>Aspirin 81mg with Dipyridamole</td>
<td>6 (6.9%)</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>63 (71.3%)</td>
</tr>
<tr>
<td><strong>Median laboratory values at GIB</strong></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>2.2</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>7.3</td>
</tr>
<tr>
<td>Change in hemoglobin</td>
<td>2.4</td>
</tr>
<tr>
<td>Platelets</td>
<td>213</td>
</tr>
<tr>
<td><strong>Product requirements</strong></td>
<td></td>
</tr>
<tr>
<td>Packed red blood cells</td>
<td>72 (82.8%)</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>9 (10.3%)</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>16 (18.4%)</td>
</tr>
<tr>
<td><strong>Median LOS (days)</strong></td>
<td>12</td>
</tr>
</tbody>
</table>
CUMC Experience: Endoscopic and therapeutic yields by GIB presentation

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number</th>
<th>Diagnostic Yield</th>
<th>Therapeutic Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGD</td>
<td>26</td>
<td>11 (42.3%)</td>
<td>6 (23.1%)</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>16</td>
<td>2 (12.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Enteroscopy</td>
<td>4</td>
<td>4 (100%)</td>
<td>3 (75%)</td>
</tr>
<tr>
<td>Capsule</td>
<td>7</td>
<td>5 (71.4%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>53</strong></td>
<td><strong>22 (41.5%)</strong></td>
<td><strong>9 (19.6%)</strong></td>
</tr>
</tbody>
</table>

Axelrad / Yuzefpolskaya JHLT 2018
CUMC Experience: Endoscopic and therapeutic yields by GIB presentation

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number</th>
<th>Diagnostic Yield</th>
<th>Therapeutic Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGD</td>
<td>8</td>
<td>1 (12.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>15</td>
<td>9 (60%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Enteroscopy</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Capsule</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>23</strong></td>
<td><strong>10 (43.5%)</strong></td>
<td><strong>3 (13%)</strong></td>
</tr>
</tbody>
</table>

Axelrad / Yuzefpolskaya JHLT 2018
CUMC Experience: Endoscopic and therapeutic yields by GI bleeding (GIB) presentation

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number</th>
<th>Diagnostic Yield</th>
<th>Therapeutic Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGD</td>
<td>36</td>
<td>13 (36.1%)</td>
<td>8 (22.2%)</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>25</td>
<td>3 (12%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Enteroscopy</td>
<td>3</td>
<td>1 (33.3%)</td>
<td>1 (33.3%)</td>
</tr>
<tr>
<td>Capsule</td>
<td>7</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>71</strong></td>
<td><strong>15 (21.1%)</strong></td>
<td><strong>12 (18.8%)</strong></td>
</tr>
</tbody>
</table>

*Axelrad / Yuzefpolskaya JHLT 2018*
CUMC Experience: Endoscopic evaluation

Total locations identified: 49

Esophagus: 0

Stomach: 19/49 (38.8%)

Duodenum: 9/49 (18.4%)

Jejunum/Ileum: 7/49 (14.3%)

Colon: 14/49 (28.6%)

Lesions

- AVM: 46%
- Erosions: 27%
- Other: 9%
- PUD: 11%
- Diverticular: 7%

Axelrad / Yuzefpolskaya JHLT 2018
CUMC Experience: Endoscopic evaluation

<table>
<thead>
<tr>
<th>Total (n=87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic evaluation</td>
</tr>
<tr>
<td>Endoscopic diagnosis</td>
</tr>
<tr>
<td>Endoscopic intervention</td>
</tr>
<tr>
<td>Rebleed within 6 months</td>
</tr>
</tbody>
</table>

Average 1.9 procedures per patient

- Multiple lesions (26, 59.1%)
## Predictors of recurrent GIB

<table>
<thead>
<tr>
<th></th>
<th>LVAD patients with one GIB (n=44)</th>
<th>LVAD patients with recurrent GIB (n=43)</th>
<th>Hazards Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product requirements</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packed red blood cells</td>
<td>33 (75%)</td>
<td>39 (90.7%)</td>
<td>2.51 [0.9, 7.05]</td>
<td>0.0801</td>
</tr>
<tr>
<td>Median number</td>
<td>2 (0.5-4.0)</td>
<td>3 (2-7)</td>
<td>1.05 [1.01, 1.09]</td>
<td>0.0073</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>3 (6.8%)</td>
<td>6 (14%)</td>
<td>2.24 [0.92, 5.47]</td>
<td>0.0752</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>8 (18.2%)</td>
<td>8 (18.6%)</td>
<td>1.22 [0.56, 2.63]</td>
<td>0.6202</td>
</tr>
<tr>
<td><strong>Endoscopic evaluation of index GIB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source identified</td>
<td>18 (40.9%)</td>
<td>26 (60.5%)</td>
<td>1.75 [0.95, 3.24]</td>
<td>0.0747</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>26 (59.1%)</td>
<td>17 (39.5%)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Upper GI tract</td>
<td>10 (22.7%)</td>
<td>20 (46.5%)</td>
<td>2.82 [1.44, 5.52]</td>
<td>0.0025</td>
</tr>
<tr>
<td>Lower GI tract</td>
<td>8 (18.2%)</td>
<td>4 (9.3%)</td>
<td>0.7 [0.24, 2.1]</td>
<td>0.5263</td>
</tr>
<tr>
<td>Upper and lower GI tract</td>
<td>0</td>
<td>2 (4.7%)</td>
<td>1.08 [0.25, 4.78]</td>
<td>0.9147</td>
</tr>
<tr>
<td><strong>Type of lesion</strong></td>
<td></td>
<td></td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>AVM</td>
<td>9</td>
<td>12</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Erosions</td>
<td>3</td>
<td>9</td>
<td>1.64 [0.68, 3.96]</td>
<td>0.2713</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>6</td>
<td>0.51 [0.18, 1.48]</td>
<td>0.2115</td>
</tr>
<tr>
<td><strong>Intervention performed</strong></td>
<td>9 (20.5%)</td>
<td>14 (53.8%)</td>
<td>1.92 [1.01, 3.66]</td>
<td>0.0480</td>
</tr>
</tbody>
</table>
Risk for re-bleed: Endoscopic intervention

- 78 pts (30%) had 158 GIBs

"Endoscopic therapy seems to mainly identify patients at the highest risk for recurrent GIB, representing a **marker for more extensive disease**, and does not address the root cause of this problem."

Source (P=0.003)
- **Intervention** during the index examination (p=0.013)
Overcoming Futility?

- A single, treatable source of bleeding is rarely identified in LVAD recipients
- Endoscopic therapy does not appear to reduce the incidence of recurrent GIB
- Management guidelines are significantly limited
Proposed Algorithm

**UPPER GIB**
Melena, coffee-ground emesis, hematemesis

Push Enteroscopy

**LOWER GIB**
Hematochezia

Colonoscopy

**OCCULT GIB**
Hemepositive brown stool, iron deficiency anemia

Initial medical management

Additional endoscopic evaluation in cases of:
- Hemodynamic instability despite administration of blood products
- Persistent GIB despite withholding or after resumption of lower-dose antithrombotic treatment
- Age-appropriate colon cancer screening
Case - 60yo M, Conventional management

ICM
HMII LVAD implanted as DT

Developed Melena
Admitted

GI called
Push enteroscopy
Performed with APC of nonbleeding jejunal AVMs

Colonoscopy performed
without source

Capsule endoscopy
performed

Melena resolves

Hgb stabilizes

Transfused 4 units pRBC
Preps for capsule
NPO

Preps for colonoscopy
NPO

AC restarted
Discharged

LOS: 5 days, pRBC: 2 units

Hgb 1.5 units below baseline
AC Held
PPI gtt initiated
Transfused 2 units pRBC
NPO

Hgb continues to decrease
Transfused 4 units pRBC

NPO

LOS: 11 days, pRBC: 6 units
Potential Benefits

- Conventional management
  - 87 initial admissions and 147 endoscopies: $2,230,609
- Proposed algorithm
  - Projected 66 endoscopies, a reduction by nearly 45%
  - Assuming that each reduction in endoscopic procedure would translate into one less day spent in the hospital, the overall estimated cost would be $1,449,414, representing a 35% savings
Conclusions

- GIB is frequent ≈ 25%, but does not impact survival
- Pathogenesis: Hematologic (antithrombotic therapy and vWF deficiency) + structural abnormalities (AVMs)
- Medical management: Stop ASA, continue AC, ACEI and Octreotide (Thalidomide)
- Endoscopic management: low diagnostic and therapeutic yield
- We propose an algorithm that may significantly reduce the number of low-yield endoscopies, LOS and costs -Prospective Results (ISHLT 2018)