Management of antithrombotic therapy in patients with LVADs

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• CME
  – American Society of Hematology

• Hematologist
Outline

• Review coagulation cascade and effect of LVADs on coagulation
• Anticoagulation in patients with LVADs
• Antiplatelet therapy in patients with LVADs
Coagulation system

Collagen

Thrombin

Tissue Factor

XIIa

Complement & Bradykinin System

XIa

XII

IX

VIII

XI

IXa

XIIa

VIIa

VII

VIIIa

V

Va

Xa

Va

X

Fibrinogen

Fibrin

Poly-P

Thrombin

Collagen
LVAD Effect on Coagulation System

**Normal**

1. Platelets Bind to VWF
2. Platelets Activate
3. Coagulation Factors Activated
4. Thrombin → Fibrin
5. Fibrinolysis

**LVAD**

1. Impaired platelet/VWF binding
   Acquired VW Disease
2. Platelets Activated
3. Decreased Contact Pathway Factors
4. Thrombin formation
5. Fibrinolytic activation

Adult LVAD Antithrombotic Therapy

50% Anticoagulated
30% Aspirin

LVAD Implantation

heparin

Day 1
heparin

aPTT Goal: 40-60 s 60-80 s
Anti-Xa: 0.2-0.4 0.4-0.7

aspirin

Chest tube removal

Vitamin K antagonist (VKA)

Heparin Mechanism of Action

Unfractionated Heparin

Complement & Bradykinin System

Tissue Factor

AT

XII → XIIa

XI → Xla

IX → IXa

VIII → VIIIa

X → Xa

Thrombin

Collagen
Perioperative Heparin

- HMII BTT retrospective review
  - Bridging: No difference in thrombosis rates
  - Less bleeding requiring transfusion in patients not treated with heparin
- Retrospective cohort, matched historical controls
  - Thrombosis: 4.9% heparin vs. 27.0% no bridging
  - Multivariate analysis: OR=0.10 (CI 0.01–0.85)
- PREVENT trial: standardized bridging
- Dr. Guglin: study of bridging around elective procedures

Heparin Monitoring

**aPTT**

- More heparin = Less colored product
- Less heparin = More colored product

**Anti-Xa**

- More heparin = Less colored product
- Less heparin = More colored product

Heparin

Antithrombin
Heparin Monitoring

- Determine if your lab adds anti-thrombin to anti-Xa assay
- aPTT assays not standardized between institutions
- aPTT activator (Kaolin) not standardized between manufactures or lots
- aPTT must be calibrated to measure anticoagulation with heparin against anti-Xa
PTT vs. anti-Xa monitoring

Discordance higher if INR> 1.5 and thrombosis/hemolysis

Warfarin Mechanism of Action

Warfarin

Complement & Bradykinin System

Vit K epoxide Reductase

Collagen
Long-term Antithrombotic Therapy

- Vitamin K antagonist treatment standard

<table>
<thead>
<tr>
<th><strong>INR Goal avg (range)</strong></th>
<th>Axial</th>
<th>Centrifugal</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-3 (1.5-3.5)</td>
<td>2-3 (2-3.5)</td>
<td></td>
</tr>
</tbody>
</table>

54% people changed warfarin dose
- 22% difference in weekly dose
- 70% decrease in dose

Managing VKA therapy

<table>
<thead>
<tr>
<th>Drug or Factor</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>40 hours</td>
</tr>
<tr>
<td>Phenprocoumon</td>
<td>144 hours</td>
</tr>
<tr>
<td>Factor VII</td>
<td>6 hours</td>
</tr>
<tr>
<td>Protein C</td>
<td>8 hours</td>
</tr>
<tr>
<td>Factor II</td>
<td>50 hours</td>
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</table>

• Will NOT see the effect of warfarin dose change for 24-36 hours

INR Intensity

- Single center retrospective review
- 249 patients
- Median follow-up: 17.6 ± 13.6 months
- Optimal INR 2.6

*Circ Heart Fail.* 2016;9:e002680
Managing VKA therapy

• Pharmacist Run Anticoagulation = Improved Time-In-therapeutic Range (TTR)
• Patient Self Management= Improved Time-In-therapeutic Range

<table>
<thead>
<tr>
<th></th>
<th>Pharmacist Management (n=11)</th>
<th>Usual Care (n=44)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTR</td>
<td>44.4%</td>
<td>30.6%</td>
<td>0.03</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.23 ppy</td>
<td>0.33 ppy</td>
<td>0.55</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>0.12 ppy</td>
<td>0.13 ppy</td>
<td>0.88</td>
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</table>

ppy=per-patient year

ASAIO Journal 2014; 60:193–198
Antiplatelet Mechanism of Action

Platelet Activation
- Thrombin
- Paracrine release of TXA, ADP, cAMP
- Aspirin ( irreversibly inhibits COX, TXA2 synthase)
- Clopidogrel, prasugrel, ticagrelor, cangrelor, ticlopidine (inhibit aggregation, ADP receptor antagonists)
- Vorapaxar (GPIIb/IIIa receptor blocker)

Platelet Adherence
- Aspirin

Platelet Aggregation
- Thrombin
- TXA2, ADP, cAMP
- Eptifibatide, abciximab, tirofiban (GPIIb/IIIa receptor blockers)
- Dipyridamole (activates adenylate cyclase, increases cAMP levels)

PAR1
Long-term Antithrombotic Therapy

- Meta-analysis: Antiplatelet therapy variable

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<thead>
<tr>
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<tr>
<td>Major Hemorrhage</td>
<td></td>
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</tr>
<tr>
<td>Aspirin</td>
<td>6-58%</td>
<td>9-44%</td>
</tr>
<tr>
<td>Aspirin + Dipyridamole</td>
<td>16-40%</td>
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Aspirin Dose

Hemorrhagic Events

<table>
<thead>
<tr>
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<tr>
<td>ASA 81</td>
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<tr>
<td>+DPE</td>
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<tr>
<td>26</td>
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<tr>
<td>17</td>
<td>21</td>
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<td>30</td>
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Thrombotic Events

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**TRACE**

**EU-TRACE**

- VKA therapy
- 91% Standard of Care
- 2-year rates (n=92)
  - Ischemic stroke=0.03 ppy
  - Device thrombosis=0.05 ppy
  - Bleeding= 0.10 ppy

**US-TRACE**

- VKA alone, ASA alone, None
- 82% enrolled due to bleeding
- 1 year Rates
  - Ischemic stroke=0.07 ppy
  - Device thrombosis=0.08 ppy
- 52% Subsequent bleeding

JHLT 2015; 34: 1542–1548.
Monitoring Anti-Platelet Medications

• 8% “non-responders” based on aggregometry

• Retrospective cohort (n=57)
  – **Goal**: TEG-MA 60-70 mmHg
  – **Regimen**: aspirin 81 → 325 → 650 mg/day + Dipyridamole (DPE) max 1 g/day
  – 68% received DPE
    • 68% received ASA + DPE
  – Bleeding 0.21 events/py

Summary

- Extreme variability in practice
- aPTT testing not standardized
- Consider use of anti-Xa testing especially in thrombosis
- VKA therapy with INR 2-3
- Limited evidence for modification of anti-platelet therapy based on testing