ASH 2018 Guidelines for Management of VTE: Heparin-Induced Thrombocytopenia and Optimal Management of Anticoagulation Therapy

Wednesday, February 20, 2019, 12:00 PM ET

Guest Speakers: Adam Cuker, MD, MS and Daniel Witt, PharmD, FCCP, BCPS

AC Forum Moderators: Tracy Minichiello, MD; Michael Streiff, MD; Diane Wirth, ANP, CACP
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American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia

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ASH 2018 VTE GUIDELINES: HIT
Importance of Heparin-induced Thrombocytopenia (HIT)

- Unfractionated heparin and low molecular weight heparin most widely used anticoagulants
  - 12 million patients treated each year
- HIT affects 1 in 5000 hospitalized patients
  - Risk varies from <0.1% to 7% depending upon
    - Preparation UFH>>LMWH
    - Patient population Surgery>Medicine
    - Duration of exposure
- HIT is associated with 50-fold increase in thrombosis risk
  - 30% to 50% suffer venous or arterial thrombosis

Cuker A et al. Blood Advances 2018;
Pathogenesis of Heparin-induced thrombocytopenia (HIT)

Step 1: Heparin binds to platelet factor 4 (PF4)
Step 2: Binding changes PF4 structure generating new antigen
Step 3: Immune system generates an antibody against new PF4 antigen
Step 4: IgG antibody crosslinks Fc receptors on platelets and monocytes causing activation
Step 5: Activated platelets and monocytes activate coagulation cascade causing thrombosis

The Clinical-Pathologic Syndrome of Heparin-induced Thrombocytopenia

- Exposure to UFH/LMWH for 5 or more days
- Platelet drop of 50% or more
- Moderate thrombocytopenia (20-100,000/µL)
- Thrombosis (venous>arterial)
  - Skin lesions (plaques, necrosis)
  - Systemic inflammatory response syndrome
- DIC

Alepally GM. Blood 2017; Warkentin TE et al. NEJM 1995
Management of Suspected Heparin-induced Thrombocytopenia

- Step 1: Assess pre-test probability
- Step 2: If intermediate or high risk, eliminate exposure and initiate alternative AC
- Step 3: Send HIT assay
- Step 4: Follow up on HIT assay results

<table>
<thead>
<tr>
<th>Variable</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute thrombocytopenia</td>
<td></td>
<td>Platelet count decrease of &gt;50% and nadir ≥20,000/mm³</td>
<td>Platelet count decrease of 30–50% or nadir 10,000–19,000/mm³</td>
</tr>
<tr>
<td>Timing of onset</td>
<td></td>
<td>Day 5–10, or day 1 if recent heparin exposure</td>
<td>&gt;Day 10 or unclear exposure</td>
</tr>
<tr>
<td>Thrombosis</td>
<td></td>
<td>New thrombosis or anaphylactoid reaction after heparin bolus</td>
<td>Progressive or recurrent thrombosis</td>
</tr>
<tr>
<td>Other cause of thrombocytopenia</td>
<td></td>
<td>None</td>
<td>Possible</td>
</tr>
<tr>
<td>Total score</td>
<td>6–8, indicating high score</td>
<td>4 or 5, indicating intermediate score</td>
<td>0–3, indicating low score</td>
</tr>
</tbody>
</table>

Important Screening Recommendations of ASH HIT Guideline

• Assess Patient Population Risk for HIT
  • Low Risk (<0.1%): Medical, obstetric and minor surgery/trauma patients receiving LMWH, any patient receiving fondaparinux- No platelet count monitoring suggested
  • Intermediate Risk (0.1%-1%) Medical or obstetric patients receiving UFH, major surgery/trauma patients receiving LMWH- Platelet count monitoring suggested every 2-3 days until day 4-14 of treatment (or day 0-14 if heparin in last 30 days)
  • High Risk (>1%): Major surgery/trauma patients receiving UFH-Platelet count monitoring suggested daily until day 4-14 of treatment (or day 0-14 if heparin in last 30 days)

Cuker A et al. Blood Advances 2018
Important Diagnosis Recommendations of ASH HIT Guideline

• Assess the patient’s pre-test probability of HIT using 4T score
• If low pre-test probability, the panel *recommends* against HIT testing (unless uncertainty about 4T score accuracy)
• If intermediate or high 4T score, the panel *recommends* HIT testing
  • *Suggests* testing with functional assay (e.g., serotonin release assay)
  • Likelihood of HIT increases with higher 4T score and higher OD value on PF4 immunoassay

Cuker A et al. Blood Advances 2018
2018 ASH HIT Diagnosis and Treatment Algorithm

Cuker A et al. Blood Advances 2018
Important Treatment Recommendations of ASH HIT Guideline

- If low 4T score (0-3 pts.), the panel *recommends* against empiric HIT treatment
- If intermediate 4T score (4-5 pts.), the panel *recommends* discontinuing heparin and *suggests* initiating alternative AC at prophylactic dose (if no reason for therapeutic AC and high risk for bleeding) or therapeutic dose (if indication for therapeutic dose or low risk for bleeding)
- If high 4T score (6-8 pts.), the panel *recommends* discontinuing heparin and initiating alternative AC at therapeutic dose
- If intermediate or high 4T score and negative immunoassay, the panel *recommends* reinitiating of heparin, if indicated
  - Consider repeat immunoassay or functional HIT assay
- If immunoassay is positive, the panel *recommends* continuing alternative AC for intermediate and high 4T score
Important Treatment Recommendations of ASH HIT Guideline

• In acute phase HIT or HIT, the panel recommends therapeutic dose alternative AC with parenteral DTI, fondaparinux or direct oral anticoagulant
  • In critically ill patients, bivalirudin or argatroban may be preferable
  • In patients with life- or limb-threatening thromboembolism, parenteral alternative AC may be preferred
  • In stable patients at low risk of bleeding, fondaparinux or DOACs are reasonable options
  • Of DOACs, most published experience with rivaroxaban
    • In HIT, prefer 15 mg BID X 3 weeks then 20 mg daily
    • In HIT, prefer 15 mg BID until platelet recovery then 20 mg daily

• Panel recommends against use of IVC filters

Cuker A et al. Blood Advances 2018
Important Treatment Recommendations of ASH HIT Guideline

• HIT without thrombosis: The panel recommends therapeutic AC until platelet count recovery at a minimum
  • Panel suggests against continuing AC ≥ 3 months unless delayed platelet recovery in setting of ongoing HIT

• HIT with thrombosis: Therapeutic AC for 3 to 6 months (no recommendation from panel on this patient group)

• The panel recommends against initiation of VKA before platelet count recovery

• The panel suggests treatment with a DOAC rather than a VKA

Cuker A et al. Blood Advances 2018
Questions for Adam Cuker MD, MS

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Laboratory Monitoring of AC

• In patients with renal dysfunction and obese patients, the panel *suggests* against LMWH monitoring to guide dose selection
  • Evidence basis/Rationale- No studies directly compared monitoring to no monitoring

• In patients taking DOACs, the panel *suggests* against lab monitoring during bleeding management
  • Evidence basis/rationale- No studies directly compared monitoring versus no monitoring when managing bleeding

Witt DM et al. Blood Advances 2018
Point-of-Care INR testing

• The panel *suggests* home POC INR self testing over other approaches except Patient Self Management (PSM)
  • Evidence: Patient Self Testing (PST) may be associated with fewer recurrent DVT/PE but is associated with higher patient satisfaction and TTR.

• The panel *recommends* Patient Self Management (PSM) over other approaches in suitable patients
  • Evidence: PSM associated with lower mortality (Relative Risk [RR] 0.58; 0.38-0.89) recurrent PE (RR 0.48; 0.32-0.71), DVT (RR 0.48; 0.32-0.71) and improved patient satisfaction.

Witt DM et al. Blood Advances 2018
Transition between anticoagulants

• For patients transitioning from DOAC to VKA, the panel *suggests* overlapping DOAC and VKA until the INR is within the therapeutic range over using LMWH or UFH
  • Evidence-3 AF DOAC RCT which monitored patient outcomes during transition from DOAC to VKA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Warfarin (N=3147)</th>
<th>High-dose edoxaban (N=3050)</th>
<th>Low-dose edoxaban (N=3107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SEE</td>
<td>5 (1.94%/y)</td>
<td>4 (1.60%/y)</td>
<td>4 (1.57%/y)</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>7 (2.71%/y)</td>
<td>7 (2.80%/yr)</td>
<td>10 (3.93%/y)</td>
</tr>
<tr>
<td>All cause Mortality</td>
<td>5 (1.94%/y)</td>
<td>5 (2.0%/y)</td>
<td>7 (2.74%/y)</td>
</tr>
</tbody>
</table>

Invasive Procedure Management: Assessing Thrombotic Risk

Table 4. VTE recurrence risk stratification

<table>
<thead>
<tr>
<th>High risk</th>
<th>Moderate risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE within past 3 mo</td>
<td>VTE within past 3-12 mo</td>
<td>VTE &gt; 12 mo previously No other risk factors</td>
</tr>
<tr>
<td>Deficiency of protein C, protein S, or antithrombin</td>
<td>Heterozygous factor V Leiden</td>
<td></td>
</tr>
<tr>
<td>Antiphospholipid antibody syndrome</td>
<td>Prothrombin 20210 mutation</td>
<td></td>
</tr>
<tr>
<td>Multiple thrombophilic abnormalities</td>
<td>Recurrent VTE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Active cancer</td>
<td></td>
</tr>
</tbody>
</table>

Witt DM et al. Blood Advances 2018
Invasive Procedure Management

For patients at low to moderate risk of recurrent VTE who require interruption of VKA therapy, the panel *recommends* against peri-procedural bridging with LMWH or UFH.

- Evidence from two studies (Clark NP JAMA IM 2015 and Birnie DH NEJM 2013) indicate low risk of recurrent event (3 of 1755; 0.17%) and increased risk of bleeding (RR 31.73 [4.14-243.19]; Absolute RR 25 bleeds more per 1000 [3 more to 196 more]).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Bridge</th>
<th>No Bridge</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>13/519 (2.5%)</td>
<td>1/1236 (0.08%)</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>0/519</td>
<td>3/1236 (0.24%)</td>
<td>P=NS</td>
</tr>
</tbody>
</table>

Management of AC-related Bleeding

• For life-threatening bleeding during VKA therapy, the panel suggests a 4 factor PCC rather than FFP in addition to cessation of VKA and IV Vitamin K
  • 4F-PCC increased the proportion of patients with INR ≤1.2 to 1.3 within 0.5 to 3 hours (RR 6.66 [3.82-11.61]) and reduced volume overload (RR 0.34 [0.13-0.85] ARR 107 fewer volume overload episodes per 1000 [24 to 141 fewer]) with no impact on mortality
  • 4F-PCC possibly increased the risk of ICH or hematoma expansion, PE, DVT and any TE risk although risk confidence intervals overlapped 1.

Witt DM et al. Blood Advances 2018
Sarode R et al. Circulation 2013
Steiner T et al Lancet Neurol 2016
Management of AC-related Bleeding

• For life-threatening bleeding with Xa DOAC, the panel *suggests* using 4F-PCC in addition to cessation or cessation alone
  • Evidence does not allow conclusion to be made as to benefits and risks of the two options since there are no comparative studies

• For life-threatening bleeding with Xa DOAC, the panel *suggests* usingandexanet alfa in addition to cessation
  • Evidence does not allow conclusions to be made as to benefits and risks of andexanet alfa since there are no comparative studies

• For life-threatening bleeding with Dabigatran, the panel *suggests* using idarucizumab in addition to cessation
  • Evidence does not allow conclusion to be made as to benefits and risks of idarucizumab since there are no comparative studies

Witt DM et al. Blood Advances 2018
Resumption of Anticoagulation after Bleeding

- For patients at moderate to high risk of VTE and not at high risk of bleeding who require long-term or indefinite AC, the panel suggests resumption of AC within 90 days.

  - Evidence from 17 observational studies found that resumption of AC after ICH or GI bleed was associated with a reduced risk of all-cause mortality (RR 0.62 [0.43-0.89] Absolute RR 165 fewer deaths per 1000 [247 to 48 fewer]) and thromboembolism (RR 0.45 [0.25-0.83] Absolute RR 58 fewer TE per 1000 [80 to 18 fewer]).

  - Resumption of AC was associated with an increased risk of major bleeding (RR 1.57 [1.12-2.27] Absolute RR 43 more bleeding events per 1000 [9 more to 92 more]).

- Panel felt waiting at least 14 days but not more than 90 days to resume AC is reasonable.
Questions for Dan Witt, PharmD, FCCP, BCPS

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