EMERGENT REVERSAL OF ANTIPLATELETS AND ANTICOAGULANTS

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OBJECTIVES

• Understand why reversal of antiplatelets and anticoagulants is a growing concern in trauma

• Identify the strengths and limitations of available data for reversal agents

• Develop a management strategy for anticoagulant reversal
THE FACE OF TRAUMA IS CHANGING

• The average age of trauma is increasing

• Older patients have more comorbidities and more medications

• Medication evaluation is recommended as part of the primary survey for geriatric trauma
  — Antiplatelets
  — Anticoagulants

Adams AD, Holcomb JB. Curr Opin Crit Care 2015
ACS TQIP Geriatric Management Guidelines
National Trauma Data Bank 2016 Annual Report (American College of Surgeons)
MORTALITY INCREASES WITH AGE

CASE FATALITY RATE (%)

<1  5  10  15  20  25  30  35  40  45  50  55  60  65  70  75  80  85  90

year

AGE

National Trauma Data Bank 2016 Annual Report (American College of Surgeons)
Aspirin remains the drug of choice for primary prevention of coronary heart disease events in patients with risk factors.

- 2016 AHA updated recommendations for dual antiplatelet therapy (DAPT) duration in CAD:
  - "Should be given" in most clinical settings for at least 6–12 months
  - "May be reasonable" to continue DAPT beyond the initial 6-12 months
  - "Necessitates a fundamental tradeoff between decreasing ischemic risk and increasing bleeding risk"
ANTIPLATELET AGENTS

Aspirin

P2Y₁₂ Inhibitors *clopidogrel, ticagrelor, prasugrel*
ASPIRIN

P2Y₁₂ Inhibitors clopidogrel, ticagrelor, prasugrel
MEASURING ANTIPLATELET EFFECT

- Platelet count
- Maximum amplitude

- TEG-PM or ROTEM-PM (Platelet Mapping)
- VerifyNow – assays for aspirin or P2Y$_{12}$

Bachelani AM, et al. Surgery 2011
Lam, et al. Cureus 2018
ANTIPLATELET REVERSAL

• Platelet Transfusion
  – May be over exposing patients to platelets
  – Significantly decreased platelet inhibition from ASA (76% to 52.7%, p<0.01), but not clopidogrel (64.5% to 48.4%, p=0.07)
  – Dose-response relationship
  – Risks vs. benefits of platelet administration
    – Not associated with change in clinical outcomes (CT score, length of stay, mortality)
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  – Risks vs. benefits of platelet administration
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Neurocritical Care/SCCM Guidelines –
“Suggest against platelet transfusion who will not undergo a neurosurgical intervention”
“Suggest platelet transfusion in those that will”
“Recommend platelet function testing”
Desmopressin (DDAVP)

- Promotes platelet adhesion by increasing von Willebrand Factor
- Small, retrospective studies have shown improved platelet aggregation
- Mixed results on effect on hemorrhage progression
- Dose range 0.3 – 0.4 mcg/kg
- Often given in combination with platelet transfusions
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Neurocritical Care/SCCM Guidelines –
“Suggest consideration of a single dose of desmopressin in ICH (0.4 μg/kg IV)”
“Can be used in addition to platelet transfusion in patient that will undergo a neurosurgical procedure”

Naidech, et al. Stroke 2014
ANTIPLATELET REVERSAL

- 200 patients with TBI and evidence of platelet dysfunction using VerifyNow
- 74 received desmopressin and 54 received platelets; compared to no intervention
  - Rates of ICH progression were similar
  - Lower discharge GCS and GOS

- Desmopressin and platelet transfusions were not protective against poor outcomes in logistic regression analysis
VITAMIN K ANTAGONISTS

Warfarin
VITAMIN K ANTAGONISTS

Warfarin
WARFARIN MONITORING & REVERSAL

- Warfarin monitoring – INR
- Vitamin K
- FFP
- Prothrombin complex concentrate
- Recombinant Factor VIIa
WARFARIN MONITORING & REVERSAL

- Warfarin monitoring – INR
- Vitamin K

ACC/AHA Guidelines –
“Administer weight/INR based 4F-PCC OR fixed-dose (1000 units for non-ICH and 1500 units for ICH)”
“If 4F-PCC not available, use FFP 10-15 mL/kg”
• 3 vs. 4 Factor
• Activated (FEIBA) vs. non-activated (Kcentra)
• Why vitamin K is still necessary
• Fixed dose vs. weight/INR based
# FDA DOSING RECOMMENDATIONS

<table>
<thead>
<tr>
<th>INR</th>
<th>Weight-based dose</th>
<th>Max total dose</th>
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<tbody>
<tr>
<td>2 to &lt; 4</td>
<td>25 units/kg</td>
<td>2500 units</td>
</tr>
<tr>
<td>4 to 6</td>
<td>35 units/kg</td>
<td>3500 units</td>
</tr>
<tr>
<td>&gt; 6</td>
<td>50 units/kg</td>
<td>5000 units</td>
</tr>
</tbody>
</table>
FIXED DOSE PCC

• Strategy to improve time to administration
• Later recognized as effective and cost savings
• Doses range from 1000-2000 units with ability to re-dose if needed
• Most studies show acceptable reversal
  • INR goal < 1.5: ~65-75%
  • INR goal < 2: > 90%
DIRECT THROMBIN INHIBITORS

Dabigatran
DIRECT THROMBIN INHIBITORS

Dabigatran
DTI MONITORING

• Qualitative Tests
  • Thrombin time (TT)*
  • aPTT

• Quantitative Tests
  • Dilute thrombin time (dTT)
  • Ecarin clotting time (ECT)
DTI REVERSAL

- Idarucizumab (Praxbind®)
  - Monoclonal antibody specific for dabigatran
  - 350x affinity for dabigatran than thrombin

- PCC or aPCC
DTI REVERSAL

• Idarucizumab (Praxbind®)
  – Monoclonal antibody specific for dabigatran

ASH AC Forum Guidelines –
  “Suggest idarucizumab”
  “If idarucizumab not available, suggest aPCC”
DTI REVERSAL

- Idarucizumab (Praxbind®)
  - Monoclonal antibody specific for dabigatran

**ACC/AHA Guidelines** –

“Administer 5g idarucizumab”

“If idarucizumab not available, use PCC or aPCC”

Cucker, et al. AJH 2019
Tomaselli, et al. JACC 2020
REVERSE-AD

- 503 patients
  - 301 uncontrolled bleeding, 202 urgent procedure
  - 45.5% GI bleed, 32.6% intracranial hemorrhage
- Median time to bleeding cessation 2.5 hours
- Median time to initiation of procedure 1.6 hours
- Thrombotic events 6.3% in bleeding group, 7.4% in urgent procedure group
- Overall mortality 18.8%

- No comparator group
REVERSE-AD

C  Ecarin Clotting Time in Group A

D  Ecarin Clotting Time in Group B

Rivaroxaban, Apixaban, Edoxaban
FACTOR Xa INHIBITORS
Rivaroxaban, Apixiban, Edoxaban
Xa INHIBITOR MONITORING

• Qualitative Tests
  • INR
  • UFH or LMWH Anti-FXa*

• Quantitative Tests
  • Anti-FXa calibrated to specific agent
Xa INHIBITOR REVERSAL

- FFP
- PCC

- Andexanet alfa (Andexxa®)
  - Decoy for Xa inhibitors
  - Irreversibly binding

www.andexxa.com, accessed 5/28/19
ANEXXA-4

- Prospective, open-label, single-group
- Multicenter (63 hospitals in North America and Europe)
- 352 patients with acute major bleeding on Xa inhibitors within 18 hours of presentation
  - 64% ICH, 26% GIB
- Excellent hemostasis achieved in 82%
- Thrombotic events 10%, mortality 14%

ANEXXA-4

- Prospective, open-label, single-group
- Multicenter (63 hospitals in North America and Europe)

**ASH AC Forum Guidelines** –
"We suggest treatment with andexanet alfa. If andexanet alfa is not available, we suggest treatment with four-factor PCC 2000 units"

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**ACC/AHA Guidelines –**

“Administer andexanet alfa
If andexanet alfa is not available, administer PCC or aPCC”

Cucker, et al. AJH 2019
Tomaselli, et al. JACC 2020
WHY DOESN’T MY HOSPITAL HAVE ANDEXANET ALFA?
WHY DOESN’T MY HOSPITAL HAVE ANDEXANET ALFA?

• Product availability and cost
• Criticisms of the trial
• Viable alternative = 4 Factor PCC
  – Meta-analysis (n=340)
    • 69-77% achieved successful bleeding management
    • Crude mortality 16%
    • Thromboembolism 4%
  – On-going trial (estimated completion 2024)
    • Andexanet alfa vs. usual care
ANDEXANET ALFA DURATION OF EFFECT

A WORD OF CAUTION...

- Little is known about the safety of administering andexanet alfa and PCC

- Case series have been published (n=28)
  - 10 patients (36%) had a thromboembolic event
  - Venous and arterial events are reported
THE NEXT BIG THING?

Ciraparantag (originally PER977)
- Small, synthetic, water-soluble
- Able to bind heparins, Xa inhibitors, and oral DTIs
- Currently planning for Phase III studies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Binding sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>✓  ✓</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>✓  ✓  ✓</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>✓  ✓</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>✓  ✓  ✓</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>✓  ✓  ✓</td>
</tr>
<tr>
<td>UFH or LMWH</td>
<td>✓  ✓  ✓</td>
</tr>
</tbody>
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Ciraparantag

CONCLUSIONS

• Geriatric trauma is increasing in incidence and therefore the need for anticoagulant reversal is as well
• Anticoagulant reversal is a rapidly evolving area with new drug development
• Initial studies of new reversal agents have significant limitations and high drug cost
• Pharmacologic reversal should be guided by bleeding severity
QUESTIONS?