ACS: Bleeding Risk, Bleeding and Clinical Outcomes

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Clinical Chief of Cardiology
Clinical Professor of Medicine
OHSU
Conflict of Interest

• I DO Not Have any relevant financial relationships to disclose.

• I will stay within evidence-based guidelines and away from commercial recommendations.
Clinical Case

• 76 year old woman admitted with intermittent chest discomfort
• Past Med Hx: diabetes, dyslipidemia, obesity, TIA
• Outpatient medications: Aspirin 81 mg daily
  Simvastatin
  Metformin
  Glipizide
• Physical exam:
Vitals: 185 lbs, HR 92, BP 148/80
Clear lungs
Cor: nonpalpable PMI, RRR, quiet S1 and S2, no murmurs, normal JVP
Abd: obese
Ext: no edema, 1 plus pulses
• Labs:
  troponin I  5.6
  HCT        32%
  Platelets  168,000
  Creat      1.4 (creat clearance of 30 ml/min)
Management Strategy

• What medical therapies?
  1. Antiplatelet:
     a. Aspirin
     b. Clopidogrel
     c. Prasugrel
     d. Ticagrelor
     e. iv glycoprotein 2b/3a inhibitor

• Antithrombotic therapies?
  1. Unfractionated Heparin
  2. Low molecular Heparin
  3. Fondaparinux
  4. Bivalirudin
What is Her Bleeding Risk

• 1. <2%
• 2. 2-5%
• 3. 5-10%
• 4. 11-15%
• 5. > 15%
## Crusade Bleeding Variables

<table>
<thead>
<tr>
<th>Patient Variable</th>
<th>Points</th>
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<tbody>
<tr>
<td>Baseline Hct</td>
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<tr>
<td>Creatinine Clearance</td>
<td>0-39</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>0-11</td>
</tr>
<tr>
<td>Female Gender</td>
<td>9</td>
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<tr>
<td>CHF</td>
<td>7</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>6</td>
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<tr>
<td>Systolic Blood Pressure</td>
<td>1-10</td>
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</tbody>
</table>
# Crusade Bleeding Score/Risk

<table>
<thead>
<tr>
<th>Score</th>
<th>Bleeding Risk</th>
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<tbody>
<tr>
<td>&lt;20</td>
<td>3.1%</td>
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<tr>
<td>21-30</td>
<td>5.5%</td>
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<tr>
<td>31-40</td>
<td>8.6%</td>
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<tr>
<td>41-50</td>
<td>11.9%</td>
</tr>
<tr>
<td>&gt;50</td>
<td>19.5%</td>
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</tbody>
</table>
## Crusade Bleeding Score/Risk

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<tr>
<td>41-50</td>
<td>11.9%</td>
</tr>
<tr>
<td>&gt;50</td>
<td>19.5%</td>
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</table>

<table>
<thead>
<tr>
<th>Patient Score</th>
<th>Patient Bleeding Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCT 34 (3)</td>
<td>19.5%</td>
</tr>
<tr>
<td>CrCl 30 (35)</td>
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<tr>
<td>HR 92 (6)</td>
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<tr>
<td>Female (8)</td>
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<tr>
<td>TIA (6)</td>
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<tr>
<td>Diabetes (6)</td>
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<tr>
<td>SBP 148 (1)</td>
<td></td>
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</tbody>
</table>
Crusade

![Bar chart showing major bleeding (%) in different risk of bleeding categories for <2 Anti-thrombotics and 2 or more Anti-thrombotics.]

- **Very Low**: 1.9% (black) vs. 3.1% (white)
- **Low**: 2.6% (black) vs. 5.5% (white)
- **Moderate**: 5.3% (black) vs. 8.4% (white)
- **High**: 6.7% (black) vs. 12.0% (white)
- **Very High**: 13.5% (black) vs. 19.9% (white)
Crusade: In-Hospital Mortality

![Bar chart showing in-hospital mortality percentages for different levels of risk of bleeding.]

- Very Low: 0.2%
- Low: 0.8%
- Moderate: 1.6%
- High: 3.2%
- Very High: 6.0%
- Bleed: 9.2%
- No Bleed: 11.0%
Ischemic Events

N = 34,146
OASIS Registry,
OASIS 2, CURE trials

Death
HR, 5.37 (3.97-7.26)

MI
HR, 4.44 (3.16-6.24)

Stroke
HR, 6.46 (3.54-11.79)

- Blue: No Major Bleed
- Red: Major Bleed
Less Bleeding Is Associated With Improved Survival

OASIS-5\textsuperscript{[a]}

- Lower bleeding in fondaparinux group vs enoxaparin group: 2.2% vs 4.1%; HR, 0.52 (95% CI, 0.44-0.61)
- Lower mortality in fondaparinux group: 6.5% vs 5.8% ($P = .05$)

HORIZONS-AMI\textsuperscript{[b]}

- Lower bleeding in bivalirudin group vs UFH/GP IIb/IIIa inhibitors: 4.9% vs 8.3%, $P < .001$
- Lower cardiac-related mortality in bivalirudin group persisted at 1 year (2.1% vs 3.8%; HR, 0.57 [95% CI, 0.38-0.84], $P =$
Interaction of Patient Variables, Medical Therapies and Procedural Variables

**Pharmacology**
- UFH
- Enoxaparin
- Fondaparinux
- Bivalirudin
- Aspirin
- Clopidogrel
- Prasugrel
- Ticagrelor
- IV 2b3a inhibitors

**Procedure**
- Access site
- Smaller sheaths
- Mechanical Closure Devices
- Minimize Bridging
- Minimize duration of antithrombotics

**Patient Variables**
- Calculate Risk Score
• What medical therapies would you recommend on this patient?
Acuity

**Net Clinical Outcome**

![Graph showing cumulative net clinical outcome over days after randomization for different groups (Heparin + GP IIb/IIIa inhibitor, Bivalirudin + GP IIb/IIIa inhibitor, and Bivalirudin alone).]

- **Bivalirudin + GP IIb/IIIa inhibitor, 11.9%, P=0.89**
- **Heparin + GP IIb/IIIa inhibitor, 11.9%**
- **Bivalirudin alone, 10.3%, P=0.014**

**No. at Risk**

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</thead>
<tbody>
<tr>
<td>Heparin + GP IIb/IIIa inhibitor</td>
<td>4603</td>
<td>4172</td>
<td>4091</td>
<td>4054</td>
<td>4030</td>
<td>3992</td>
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<tr>
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<td>4084</td>
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<tr>
<td>Bivalirudin alone</td>
<td>4612</td>
<td>4246</td>
<td>4173</td>
<td>4133</td>
<td>4112</td>
<td>4065</td>
<td>3614</td>
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</table>
Composite Ischemia

Cumulative Composite Ischemia (%)

Days after Randomization

No. at Risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>At Risk</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
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<tbody>
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<td>4351</td>
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<td>4201</td>
<td>3708</td>
<td>2543</td>
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<tr>
<td>Bivalirudin + GP IIb/IIIa inhibitor</td>
<td>4604</td>
<td>4329</td>
<td>4265</td>
<td>4235</td>
<td>4215</td>
<td>4179</td>
<td>3719</td>
<td>2585</td>
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<tr>
<td>Bivalirudin alone</td>
<td>4612</td>
<td>4330</td>
<td>4276</td>
<td>4236</td>
<td>4218</td>
<td>4170</td>
<td>3708</td>
<td>2521</td>
<td></td>
</tr>
</tbody>
</table>

Bivalirudin + GP IIb/IIIa inhibitor, 7.9%, P=0.37
Bivalirudin alone, 8.0%, P=0.30
Heparin + GP IIb/IIIa inhibitor, 7.4%
Acuity Major Bleeding

Major Bleeding

Cumulative Major Bleeding (%)

Days after Randomization

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin + GP IIb/IIIa inhibitor</td>
<td>4603</td>
<td>4336</td>
<td>4282</td>
<td>4258</td>
<td>4240</td>
<td>4208</td>
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<td>2575</td>
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<tr>
<td>Bivalirudin + GP IIb/IIIa inhibitor</td>
<td>4604</td>
<td>4329</td>
<td>4286</td>
<td>4266</td>
<td>4250</td>
<td>4222</td>
<td>3761</td>
<td>2625</td>
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<tr>
<td>Bivalirudin alone</td>
<td>4612</td>
<td>4423</td>
<td>4389</td>
<td>4366</td>
<td>4352</td>
<td>4312</td>
<td>3846</td>
<td>2633</td>
</tr>
</tbody>
</table>

Heparin + GP IIb/IIIa inhibitor, 5.7%
Bivalirudin + GP IIb/IIIa inhibitor, 5.3%, P=0.41
Bivalirudin alone, 3.1%, P<0.001
Influence of Bleeding Severity Within 30 Days After PCI on the Risk for Death Over 1 Year
Baseline covariate-adjusted time-update Cox multivariable model

<table>
<thead>
<tr>
<th>Type of Bleed</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Attributable deaths within 1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI major bleed*</td>
<td>4.85 (3.56-6.60)</td>
<td>&lt;.001</td>
<td>53</td>
</tr>
<tr>
<td>ACUITY major (non-TIMI major) bleed with transfusion*</td>
<td>2.98 (2.10-4.24)</td>
<td>&lt;.001</td>
<td>40</td>
</tr>
<tr>
<td>ACUITY major (non-TIMI major) bleed without transfusion*</td>
<td>1.79 (1.09-2.93)</td>
<td>.02</td>
<td>17</td>
</tr>
<tr>
<td>Hematoma ≥ 5 cm only</td>
<td>1.30 (0.58-2.92)</td>
<td>.53</td>
<td>6</td>
</tr>
</tbody>
</table>

*Excluding hematomas, each patient is represented only once according to their most severe bleed.
## Oral Antiplatelet Therapies

<table>
<thead>
<tr>
<th></th>
<th>Primary Endpoint (CVD, MI, CVA)</th>
<th>Non CABG Major Bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA vs ASA/Clopidogrel</td>
<td>11.4% vs 9.3%*</td>
<td>1.34% vs 3.6%*</td>
</tr>
<tr>
<td>Clopidogrel/ASA vs Prasugrel/ASA</td>
<td>12.1% vs 9.9%*</td>
<td>1.8% vs 2.4%*</td>
</tr>
<tr>
<td>Prasugrel/ASA vs Ticagrelor/ASA</td>
<td>11.7% vs 9.8%*</td>
<td>3.8% vs 4.5%*</td>
</tr>
</tbody>
</table>

* p<0.05
Early ACS: Impact of Early 2b/3a inhibitors in addition to Clopidogrel

- **TIMI Major Bleeding**
  - Upstream Clopidogrel: 1.54 (1.07–2.24)
  - No Clopidogrel: 1.13 (0.69–1.84)

- **GUSTO Severe or Any RBC Transfusion**
  - Upstream Clopidogrel: 1.41 (1.07–1.87)
  - No Clopidogrel: 1.26 (1.03–1.54)

- **Transfusion**
  - Upstream Clopidogrel: 1.38 (1.04–1.83)
  - No Clopidogrel: 1.23 (1.01–1.51)
RIVAL Study Design

Key inclusions:
- Intact dual circulation of hand
- Interventionalists experienced with both (≥ 50 radial procedures in last year)

NSTE-ACS or STEMI
N = 7021

Radial access
n = 3507
UA (%) 44.3
NSTEMI (%) 28.5
STEMI (%) 27.2

Femoral access
n = 3514
UA (%) 45.7
NSTEMI (%) 25.8
STEMI (%) 28.5

Blinded adjudication of outcomes

Primary outcome: death, MI, stroke, or non-CABG-related major bleeding at 30 days
### Primary Outcome:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Radial n = 3507 (%)</th>
<th>Femoral n = 3514 (%)</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI, stroke, non-CABG major bleed</td>
<td>3.7</td>
<td>4.0</td>
<td>0.92</td>
<td>0.72-1.17</td>
<td>.50</td>
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</tbody>
</table>

### Secondary Outcomes:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Radial n = 3507 (%)</th>
<th>Femoral n = 3514 (%)</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, MI, stroke</td>
<td>3.2</td>
<td>3.2</td>
<td>0.98</td>
<td>0.76-1.28</td>
<td>.90</td>
</tr>
<tr>
<td>Non-CABG major bleed</td>
<td>0.7</td>
<td>0.9</td>
<td>0.73</td>
<td>0.43-1.23</td>
<td>.23</td>
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</tbody>
</table>
## RIVAL: Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Radial n = 3507 (%)</th>
<th>Femoral n = 3514 (%)</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Death, MI, stroke, non-CABG major bleed</td>
<td>3.7</td>
<td>4.0</td>
<td>0.92</td>
<td>0.72-1.17</td>
<td>.50</td>
</tr>
<tr>
<td><strong>Secondary Outcomes:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Death, MI, stroke</td>
<td>3.2</td>
<td>3.2</td>
<td>0.98</td>
<td>0.76-1.28</td>
<td>.90</td>
</tr>
<tr>
<td>• Non-CABG major bleed</td>
<td>0.7</td>
<td>0.9</td>
<td>0.73</td>
<td>0.43-1.23</td>
<td>.23</td>
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</tbody>
</table>
RIVAL: Other Outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>Radial</th>
<th>Femoral</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Major vascular complications</td>
<td>1.4</td>
<td>3.7</td>
<td>0.37</td>
<td>0.27-0.52</td>
<td>&lt; .0001</td>
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<tr>
<td>Death</td>
<td>1.3</td>
<td>1.5</td>
<td>0.86</td>
<td>0.58-1.29</td>
<td>.47</td>
</tr>
<tr>
<td>MI</td>
<td>1.7</td>
<td>1.9</td>
<td>0.92</td>
<td>0.65-1.31</td>
<td>.65</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.6</td>
<td>0.4</td>
<td>1.43</td>
<td>0.72-2.83</td>
<td>.30</td>
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<tr>
<td>Stent thrombosis</td>
<td>0.7</td>
<td>1.2</td>
<td>0.63</td>
<td>0.34-1.17</td>
<td>.14</td>
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<tr>
<td>Access site cross-over</td>
<td>7.6</td>
<td>2.0</td>
<td>3.82</td>
<td>2.93-4.97</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>
RIVAL: Sites of Non-CABG Major Bleeds

- Access Site: 32%
- Non-Access Site*: 68%

*Sites of non-access site bleed: gastrointestinal (most common site), intracranial, pericardial

Definitions: Major Bleeding (CURRENT/OASIS 7)
- Fatal
- Blood transfusion ≥ 2 units
- Hypotension requiring inotropes
- Leading to hemoglobin drop of ≥ 5 g/dL
- Requiring surgical intervention
- ICH or intraocular bleeding leading to significant vision loss
<table>
<thead>
<tr>
<th>Therapy</th>
<th>Radial (n = 3507) (%)</th>
<th>Femoral (n = 3514) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>99.2</td>
<td>99.3</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>96.0</td>
<td>95.6</td>
</tr>
<tr>
<td>LMWH</td>
<td>51.5</td>
<td>51.8</td>
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<tr>
<td>UFH</td>
<td>33.3</td>
<td>31.6</td>
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<tr>
<td>Fondaparinux</td>
<td>10.9</td>
<td>10.8</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>2.2</td>
<td>3.1</td>
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<tr>
<td>GP IIb/IIIa inhibitors</td>
<td>25.3</td>
<td>24.0</td>
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</tbody>
</table>
Antithrombotic Use

France:
- Enoxaparin, fondaparinux, bivalirudin, UFH

Canada:
- Fondaparinux, LMWH, UFH, bivalirudin, GP IIb/IIIa inhibitors

United States:
- Primarily bivalirudin
Conclusions

- Radial approach requires training and practice
- Patients prefer radial access
- Fewer vascular complications with radial access
- Most benefit from radial approach is in patients at risk for bleeding; reduction in bleeding = mortality benefit

Need to adopt a global bleeding reduction approach with both pharmacologic and procedural methods.
Therapy in REPLACE-2, ACUITY, and HORIZONS-AMI

17,393 PCI patients

Non-access site bleeding:
• 2/3 of all TIMI bleeding events
• Associated with a 4-fold increase in 1-year mortality

Use of bivalirudin compared with heparin + GP IIb/IIIa inhibitor significantly decreases non-access site and access site bleeding events by approximately 40%.
HORIZONS

3602 pts with STEMI

Randomized

UFH + GP IIb/IIIa
n = 1802

30
Not true MI

1-Year FU Eligible

n = 1772

26
Withdraw

13
Lost to FU

1-Year FU

n = 1733 (97.8%)

17
Withdraw

90
Lost to FU

3-Year FU

n = 1626 (91.7%)

Bivalirudin
n = 1800

29

1-Year FU

n = 1771

22

3-Year FU

n = 1730 (97.7%)

18

90
Lost to FU

n = 1634 (92.3%)
HORIZONS: 3-Year Major Bleeding (non-CABG)*

- **Bivalirudin alone (n = 1800)**
  - 1 yr HR [95%CI] = 0.62 [0.49, 0.79]
  - 3 yr HR [95%CI] = 0.64 [0.51, 0.80]
  - P < .001

- **Heparin + GP IIb/IIIa (n = 1802)**
  - Major Bleeding (%)
  - 10.5%
  - 9.4%
  - 6.9%
  - 6.0%

Number at risk
- Bivalirudin alone: 1800, 1601, 1572, 1544, 1523, 1485, 1402, 1039
- Heparin + GP IIb/IIIa: 1802, 1534, 1509, 1465, 1442, 1402, 957

* Intracranial, intraocular, retroperitoneal, access site bleed requiring intervention/surgery, hematoma ≥ 5 cm, hgb ↓ ≥ 3 g/dL with or ≥ 4 g/dL w/o overt source; reoperation for bleeding; or blood product transfusion
HORIZONS: 3-Year Mortality: Cardiac and Noncardiac

Heparin + GP IIb/IIIa (n = 1802)

1-yr HR [95% CI] = 0.57 [0.38, 0.84]
P = .004

3-yr HR [95% CI] = 0.56 [0.40, 0.80]

Cardiac Mortality (%)

Bivalirudin alone (n = 1800)

1-yr HR [95% CI] = 1.20 [0.65, 2.20]
P = .56

3-yr HR [95% CI] = 1.11 [0.74, 1.65]

Noncardiac Mortality (%)

Number at risk

<table>
<thead>
<tr>
<th>Months</th>
<th>Heparin+GP IIb/IIIa</th>
<th>Bivalirudin alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1802</td>
<td>1800</td>
</tr>
<tr>
<td>3</td>
<td>1689</td>
<td>1689</td>
</tr>
<tr>
<td>6</td>
<td>1660</td>
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<tr>
<td>9</td>
<td>1633</td>
<td>1633</td>
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<tr>
<td>12</td>
<td>1611</td>
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<tr>
<td>15</td>
<td>1574</td>
<td>1574</td>
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<tr>
<td>18</td>
<td>1525</td>
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<tr>
<td>21</td>
<td>1506</td>
<td>1506</td>
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<tr>
<td>24</td>
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<tr>
<td>27</td>
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<tr>
<td>36</td>
<td>1414</td>
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Number at risk

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<th>Heparin+GP IIb/IIIa</th>
<th>Bivalirudin alone</th>
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<tbody>
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<td>1432</td>
</tr>
<tr>
<td>36</td>
<td>1414</td>
<td>1414</td>
</tr>
</tbody>
</table>
Possible Mechanisms Linking Hemorrhagic Complications to Mortality

- Blood transfusions depleted in NO ⇄ systemic inflammation, vasoconstriction, apoptosis
- Volume depletion ⇄ ischemia, hypotension, arrhythmias
- Discontinuation of lifesaving medications (antiplatelet agents, beta-blockers, ACE inhibitors, statins)
- Complications from procedures to manage bleeding
Premier: Discharge Meds in AMI complicated by Bleeding
Continuation of Low-Dose Aspirin in Peptic Ulcer Bleeding: A Randomized Trial

<table>
<thead>
<tr>
<th></th>
<th>Aspirin n = 78</th>
<th>Placebo n = 78</th>
<th>P</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent ulcer bleeding</td>
<td>10.3%</td>
<td>5.4%</td>
<td>.25</td>
<td>1.9 (0.6-6.0)</td>
</tr>
<tr>
<td>within 30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.3%</td>
<td>12.9%</td>
<td>.005</td>
<td>0.2 (0.06-6.0)</td>
</tr>
<tr>
<td>Mortality rates (CV,</td>
<td>1.3%</td>
<td>10.3%</td>
<td>.016</td>
<td>0.2 (0.05-.70)</td>
</tr>
<tr>
<td>cerebrovascular, or GI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>complications)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All patients received a 72-hour infusion of pantoprazole followed by oral pantoprazole.
Clopidogrel and Omeprazole in CAD

NEJM 363;20

- Patients receiving dual antiplatelet tx were randomized to omeprazole or placebo.
- Primary endpoint: first occurrence of upper GI clinical events including:
  a. UGI bleed
  b. Confirmed ulcer
  c. Gastroduodenal erosions/obstruction
  d. Perforation
<table>
<thead>
<tr>
<th>Event</th>
<th>Omeprazole (N = 1876)</th>
<th>Placebo (N = 1885)</th>
<th>Event Rate (95% CI)</th>
<th>Log-Rank P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients with event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite of GI events</td>
<td>13</td>
<td>38</td>
<td>1.1 (0.4–1.8)</td>
<td>2.9 (1.9–3.9)</td>
</tr>
<tr>
<td>Overt gastroduodenal bleeding</td>
<td>1</td>
<td>8</td>
<td>0.1 (0.0–0.3)</td>
<td>0.6 (0.1–1.0)</td>
</tr>
<tr>
<td>Overt upper GI bleeding of unknown origin</td>
<td>1</td>
<td>7</td>
<td>0.1 (0.0–0.3)</td>
<td>0.6 (0.1–1.1)</td>
</tr>
<tr>
<td>Occult bleeding</td>
<td>6</td>
<td>11</td>
<td>0.6 (0.0–1.2)</td>
<td>0.8 (0.3–1.3)</td>
</tr>
<tr>
<td>GI pain with underlying multiple erosive diseases</td>
<td>3</td>
<td>8</td>
<td>0.2 (0.0–0.4)</td>
<td>0.7 (0.1–1.3)</td>
</tr>
<tr>
<td>Symptomatic gastroduodenal ulcer</td>
<td>2</td>
<td>6</td>
<td>0.1 (0.0–0.2)</td>
<td>0.2 (0.0–0.5)</td>
</tr>
<tr>
<td>Cardiovascular event</td>
<td>55</td>
<td>54</td>
<td>4.9 (3.4–6.4)</td>
<td>5.7 (4.0–7.3)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>14</td>
<td>15</td>
<td>1.2 (0.5–2.0)</td>
<td>1.5 (0.6–2.4)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>42</td>
<td>45</td>
<td>4.0 (2.6–5.4)</td>
<td>4.6 (3.1–6.1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>4</td>
<td>2</td>
<td>0.2 (0.0–0.5)</td>
<td>0.3 (0.0–0.7)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>5</td>
<td>3</td>
<td>0.4 (0.0–0.7)</td>
<td>0.3 (0.0–0.8)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>5</td>
<td>5</td>
<td>0.4 (0.0–0.7)</td>
<td>0.5 (0.0–1.1)</td>
</tr>
</tbody>
</table>
**Figure 1.** Kaplan–Meier Estimates of the Probability of Remaining Free of Primary Gastrointestinal Events, According to Study Group.

The event rate for the primary gastrointestinal end point at day 180 was 1.1% in the omeprazole group and 2.9% in the placebo group.
Figure 2. Kaplan–Meier Estimates of the Probability of Remaining Free of Primary Cardiovascular Events, According to Study Group.

The event rate for the primary cardiovascular end point at day 180 was 4.9% in the omeprazole group and 5.7% in the placebo group.
Steps for Minimizing Gastrointestinal Bleeding

Clopidogrel vs ASA and Esomeprazole to Prevent Recurrent Ulcer Bleeding
NEJM 2005;353:238

- Patients on ASA for CV prevention, presented with ulcer bleeding and healed were randomized to clopidogrel vs ASA plus esomeprazole.
- 90% of patients had CAD or PAD
- Primary endpoint: recurrent bleeding during 12 months follow up.
Table 2. Kaplan–Meier Estimates of the Likelihood of Recurrent Ulcer Bleeding and Lower Gastrointestinal (GI) Bleeding at 12 Months.

<table>
<thead>
<tr>
<th>Type of Bleeding</th>
<th>Probability of Bleeding (95% CI)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clopidogrel Aspirin plus Esomeprazole</td>
<td>Difference between the Groups percentage points</td>
</tr>
<tr>
<td>Recurrent ulcer bleeding</td>
<td>8.6 (4.1 to 13.1) 0.7 (0 to 2.0)</td>
<td>7.9 (3.4 to 12.4) 0.001</td>
</tr>
<tr>
<td>Lower GI bleeding</td>
<td>4.6 (1.3 to 7.9) 4.6 (1.3 to 8.0)</td>
<td>0.0 (−4.6 to 4.6) 0.98</td>
</tr>
</tbody>
</table>
Conclusion

• Patient risk of bleeding is important in selecting best therapies for treating ACS.
• Bleeding occurs more often in non access sites than access sites.
• Minimize dual antiplatelet therapy coupled with antithrombotic therapy.
• Minimize lovenox “bridging”.
• Bleeding is associated with increase in ischemic events and an increase in mortality.
• Clinical decision making in this patient population has become complex.