High quality, Prospective Registry Design: Statistical Recommendations, Issues and Answers for TREAT

INDUSTRY PERSPECTIVE

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Potential benefits of well-designed study leading to class labeling of anticoagulation in transradial PCI

- Safety
- Use
- Costs Healthcare
What are key study design issues for observational data?

- **Confounding and Bias**
  - Variations in degree of use of anticoagulants due to pre-existing patterns specific to US
  - Variations in drug administration and monitoring (potentially affect bleeding and ischemic outcomes)
  - Confounding by indication, both for drug and route PCI
  - Variations in center/operator by procedural volume, radial experience, geographic region, population size
What are key study design issues for observational data?

- **Sample size**
  - Adequate to help adjust for above issues of confounding
  - Adequate to represent less used anticoagulants in US
  - Feasibility—barriers to industry participation
    - Risk of misinterpretation of data as superiority of one anticoagulant over another
    - Risks of supporting a study of off-label use of their drug
    - Can study design adequately support uniform class labeling of anticoagulants, including theirs, in transradial PCI

- **Endpoints and definitions**
What would be the best basis for specific drug bleeding evaluation?

Possible pitfalls--Power

- Low usage patterns in US of certain anticoagulants
  - ability to precisely evaluate safety of low use drugs (wide CI around estimate of bleed)
  - ability to adequately compare transfemoral and transradial PCI bleeding risks of low use drugs
- Interaction or effect modification between drug type, PCI route, and bleeding
Opportunities for imbedded studies or pre-specified data collections

- enrich for subpopulations to improve power?
  - specific subpopulations at higher risk for bleeding
  - specific anticoagulants (?utility and/or feasibility)

- non-bleeding safety questions?

- use of platelet aggregation indices/devices, other novel markers of drug effect?
What are optimal comparators for bleeding safety and TRI?

- Site limited
  - bleeding creating vascular compromise
  - access site bleeds

- Systemic
OPC: can we pool data from other studies to add information?

- Large scale observational registry (pre-existing data)
- Bleeding data in randomized controlled antithrombotic therapy trials which have some percentage of transradial PCI
Hemorrhagic endpoints and incidence in a stable to low risk ACS population

<table>
<thead>
<tr>
<th>Variables</th>
<th>Heparin Plus Glycoprotein Ilb/IIa</th>
<th>Bivalirudin</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>123/3008 (4.1)</td>
<td>71/2993 (2.4)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Intracranial</td>
<td>2/3008 (0.1)</td>
<td>1/2993 (0)</td>
<td>&gt; .99</td>
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<tr>
<td>Retroperitoneal</td>
<td>16/3008 (0.5)</td>
<td>7/2993 (0.2)</td>
<td>.06</td>
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<tr>
<td>Vascular access puncture</td>
<td>74/3008 (2.5)</td>
<td>25/2993 (0.8)</td>
<td>&lt; .001</td>
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<tr>
<td>Gastrointestinal</td>
<td>18/3008 (0.6)</td>
<td>4/2993 (0.1)</td>
<td>.003</td>
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<tr>
<td>Genitourinary</td>
<td>6/3008 (0.2)</td>
<td>1/2993 (0)</td>
<td>.13</td>
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<tr>
<td>Related to cardiac surgery</td>
<td>18/3008 (0.6)</td>
<td>17/2993 (0.6)</td>
<td>.88</td>
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<tr>
<td>Minor bleeding</td>
<td>772/3008 (25.7)</td>
<td>400/2993 (13.4)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>TIMI bleeding criteria†</td>
<td></td>
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<td></td>
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<tr>
<td>Major bleeding</td>
<td>26/3008 (0.9)</td>
<td>19/2993 (0.6)</td>
<td>.30</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>91/3008 (3.0)</td>
<td>39/2993 (1.3)</td>
<td>&lt; .001</td>
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<tr>
<td>Any transfusion</td>
<td>76/3008 (2.5)</td>
<td>50/2993 (1.7)</td>
<td>.02</td>
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<tr>
<td>Transfusion ≥2 U</td>
<td>56/3008 (1.9)</td>
<td>39/2993 (1.3)</td>
<td>.06</td>
</tr>
<tr>
<td>Red blood cell</td>
<td>57/3008 (1.9)</td>
<td>43/2993 (1.4)</td>
<td>.17</td>
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<tr>
<td>Whole blood</td>
<td>4/3008 (0.1)</td>
<td>1/2993 (0)</td>
<td>.38</td>
</tr>
<tr>
<td>Platelets</td>
<td>18/3008 (0.6)</td>
<td>10/2993 (0.3)</td>
<td>.13</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
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<td></td>
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<tr>
<td>Platelets &lt; 100 × 10^9/μL</td>
<td>50/2863 (1.7)</td>
<td>20/2868 (0.7)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Platelets &lt; 50 × 10^9/μL</td>
<td>19/2863 (0.7)</td>
<td>8/2868 (0.3)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Abbreviation: TIMI, Thrombolysis in Myocardial Infarction trial. *Values are expressed as number/total (percentage). Denominators are corrected for missing values. †TIMI major and minor bleeding are mutually exclusive classifications.
Evolution of bleeding definitions

- TIMI major and minor bleed
- Bivalirudin studies change previous research accepted bleeding definitions
- Argue this is more updated and thus clinically relevant
- Increases statistical power (higher event rate) and difference between anticoagulants
- ACUITY definition major bleed used in new composite ‘quadruple’ endpoint
  - Major bleeding was defined as the cumulative occurrence within 25 to 35 days after randomization of intracranial or intraocular bleeding, hemorrhage at the access site requiring intervention, hematoma with a diameter of at least 5 cm, a reduction in hemoglobin levels of at least 4 g per deciliter without an overt bleeding source or at least 3 g per deciliter with such a source, reoperation for bleeding, or transfusion of a blood product.

- Is time to hemostasis, or CABG related bleeding relevant?