Selection of Endpoints, Balancing Safety & Efficacy & Selecting Patients for Enrollment

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Founder and Editor-in-Chief www.wikidoc.org
A Free Up-to-Date Copyleft Medical Textbook

Professor of Medicine Harvard Medical School
## Conflict of Interest Statement

### Present Research/Grant Funding

- Angel Medical Corporation
- Atrium Medical Systems
- Bayer Corp.
- Bristol Meyers Squibb Company
- CSL, Inc.
- Ikaria, Inc.
- Janssen Pharmaceuticals
- Johnson & Johnson Corporation
- Lantheus Medical Imaging
- Medtronic Vascular, Inc.
- Portola Pharmaceuticals
- Stealth Peptides, Inc.
- St. Jude Medical
- Volcano Corp
- Walk Vascular

### Consultant (all with moderate support)

- Atrium Medical Systems
- Baxter Healthcare
- Boehringer Ingelheim
- Bristol Myers Squibb Company
- Cardiovascular Research Foundation
- CSL Behring
- Cytori Therapeutics
- Daiichi Sankyo Company, Inc.
- Eli Lilly and Company
- Exeter Group
- Google, Inc.
- Navigant
- St. Jude Medical
- The Medicines Company
- Web MD

### Peer to Peer Communications

- Daiichi Sankyo Company, Inc
- Eli Lilly and Company
- The Medicines Company

### Consultant (with $0.00 monies received by Dr. Gibson)

- Bayer Corporation
- Janssen Pharmaceuticals
- Johnson & Johnson Corporation
- Ortho McNeil

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*Slide prepared by C. Michael Gibson, M.S., M.D.*
US Anti Coagulated Patients
Bleeding Rate by Product Prescribed
Presentations at ED with/without Admissions

<table>
<thead>
<tr>
<th></th>
<th>TOTAL</th>
<th>Lovenox</th>
<th>Coumadin</th>
<th>Xarelto</th>
<th>Eliquis</th>
<th>Pradaxa</th>
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<tbody>
<tr>
<td>Patients on Anticoagulants</td>
<td>6,775,896</td>
<td>1,076,029</td>
<td>4,305,218</td>
<td>733,026</td>
<td>33,444</td>
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<td>Patients w/ Bleeds</td>
<td>917,996</td>
<td>136,588</td>
<td>619,234</td>
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<td>Present to ER</td>
<td>344,682</td>
<td>53,013</td>
<td>238,474</td>
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<td>Bleeds w/ Admission</td>
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<td>32,879</td>
<td>159,705</td>
<td>14,305</td>
<td>148</td>
<td>20,598</td>
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<tr>
<td>Bleeds w/o Admission</td>
<td>117,047</td>
<td>20,134</td>
<td>78,769</td>
<td>8,523</td>
<td>74</td>
<td>9,547</td>
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</tr>
</thead>
<tbody>
<tr>
<td>Patients on Anticoagulants</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
</tr>
<tr>
<td>Patients w/ Bleeds</td>
<td>13.5%</td>
<td>12.7%</td>
<td>14.4%</td>
<td>8.7%</td>
<td>2.3%</td>
<td>15.5%</td>
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<tr>
<td>Present to ER</td>
<td>5.1%</td>
<td>4.9%</td>
<td>5.5%</td>
<td>3.1%</td>
<td>0.7%</td>
<td>4.8%</td>
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<td>Bleeds w/ Admission</td>
<td>3.4%</td>
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<td>3.7%</td>
<td>2.0%</td>
<td>0.4%</td>
<td>3.3%</td>
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<td>Bleeds w/o Admission</td>
<td>1.7%</td>
<td>1.9%</td>
<td>1.8%</td>
<td>1.2%</td>
<td>0.2%</td>
<td>1.5%</td>
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</tbody>
</table>

Source: Truven MARKETSCAN® Commercial, Medicare Supplemental and Medicaid Database; 12 mos ending in June 2013
Balancing Biomarker Data vs Clinical Data

Ongoing bleeding events & urgent unmet need to reverse anticoagulation

Rapid ascertainment of PK/PD Endpoints

Clinical relevance of PK/PD not well defined

Larger evaluation of clinical outcomes, but

Years to collect poorly validated / confounded clinical data in large number of centers throughout the world, delays access to therapy
A historical precedent is Digibind / DigiFab: Once drug is reversed, drug is no longer active

The primary outcome of the study was met in that serum free digoxin concentrations in all patients fell to undetectable levels following DigiFab administration. This was an expected outcome that is consistent with data in the literature showing that free digoxin concentrations fall rapidly following administration of Digibind.\(^2\) In the DigiFab trial, an independent blinded review of each patients ECG showed that 10 of the 15 patients studied had ECG abnormalities that improved within 4 hours after the DigiFab infusion. The remaining 5 patients had ECG abnormalities that were unchanged from baseline throughout the 24-hour assessment period, and in one case through the 30-day follow up period.

Both PK / PD data and a modest amount of clinical outcomes collected

Effectiveness: What Are The Appropriate PK / PD Markers in a Phase II, III, IIIb Study Design?

- Unbound Factor Xa levels ng/ml
- Anti-fXa activity ng/ml
- International Normalized Ratio (INR)
- Clinical meaning of biomarkers may differ across agents (Clinical significance of ACT with UFH may not = bivalirudin, INR of warfarin may not = NOAC)
- Local vs central lab assessment?
- Do you assess nadirs / peaks, percent change, use a threshold of activity, do you adjust for baseline?
- Is reversing PK/PD/MOA sufficient along with safety data for approval?
<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>Visible bleeding</th>
<th>Non-visible bleeding</th>
</tr>
</thead>
</table>
| **Excellent**| Cessation of bleeding ≤ 1 hour after end of infusion and no additional coagulation intervention required | **Muscular/skeletal**: pain relief or no increase in swelling or unequivocal signs of bleeding at ≤1 hour after end of infusion and condition has not deteriorated during the 24 hour period  
ICH: ≤20% increase in hematoma volume on CT scan at 24 hours  
Other (e.g. GIB): ≤10% decrease in corrected hemoglobin/hematocrit at 24 hours |
| **Good**     | Cessation of bleeding between >1 and ≤ 4 hours after end of infusion and no additional coagulation intervention required | **Muscular/skeletal**: pain relief or no increase in swelling or unequivocal signs of bleeding >1 and ≤4 hours after end of infusion and condition has not deteriorated during the 24 hour period  
ICH: >20% but ≤35% increase in hematoma volume on CT scan at 24 hours  
Other (e.g. GIB): >10 % to ≤20% decrease in corrected hemoglobin/hematocrit at 24 hours |
| **Poor**     | Cessation of bleeding >4 hours after end of infusion and/or additional coagulation intervention required | **Muscular/skeletal**: No improvement by 4 hours after end of infusion and/or condition has not deteriorated during the 24 hour period  
ICH: >35% increase in hematoma volume on CT scan at 24 hours  
Other (e.g. GIB): >20% decrease in corrected hemoglobin/hematocrit at 24 hours |
Clinical Variables That Could be Assessed

- Progression in BARC class
- Units of blood products transfused
- Evidence of microchimerism at later date
- Mean arterial pressure, pulse, cardiac output over 24 hours
- Duration of pressor support
- Hemoglobin nadir (difficult since hard to account for hemodilution, variability in baseline Hb)
Safety: Potential Adverse Outcomes Due to Reversal of Anticoagulation

- Confounded by adverse events due to the bleeding event itself (hypoperfusion etc.)

- Ischemic events (Stent thrombosis, stroke, systemic embolization, valves, conduits). Attribution to reversal drug complicated by multiplicity of mechanisms:
  - Ischemic events due to “Rebound” or excess resumption of pro-coagulant activity
  - Ischemic events due to “Resumption” of ischemic events in absence of anticoagulation
  - Ischemic events / thrombosis due to infusion of a drug that is itself pro-coagulant rather than a drug that is reversing anticoagulation
  - Ischemic events due to discontinuation of antiplatelet agents
  - Drug-related infusion allergic reactions
Safety: Potential Adverse Outcomes That Confound the Assessment of SAEs Due to Reversal of Anticoagulation

Adverse sequela of other resuscitative efforts

Vol. depletion ⇒ Hypotension, ischemia, arrhythmias

Complications from procedures to manage bleeding

Discontinuation of lifesaving medications (antiplatelet agents, beta blockers, statins)

Transfusion:

Red cells depleted of NO promote vasoconstriction, platelet aggregation and ineffective oxygen delivery, inflammation, increase viscosity, increase SVR and lower cardiac output, transfused cells may act as a nitric oxide sink, microchimerism whereby transfusion functions as a source of stem cells that engraft in the recipient

Other non-study blood products: Kcentra, FFP, Factor VII, 4 factor PCC, vitamin K
Clinical Outcomes: Balancing Efficacy and Safety

- Fatal or irreversible events after reversal:
  - “Effectiveness”
    
    Fatal bleeding, new ICH, for ICH at presentation could use Rankin score
  
  - “Safety”
    
    Fatal or irreversible tissue damage from ischemic events such as myonecrosis, ischemic stroke, embolism, immunogenicity?
What Kind of Bleeding Would be Included in a Phase III Trial Design?

There may be heterogeneity in the **risk** of the population depending upon the type of bleeding studied (ICH, trauma, spontaneous, access site / iatrogenic)

There is heterogeneity in **approach** to the bleeding patient by bleeding type: conservative watchful waiting versus urgent operation

There is heterogeneity in **type / and specific drug** patient is on that precipitated bleed. Variable numbers of FXa inhibitors will be enrolled, can results be generalized to entire class including drugs not yet approved?

Do you study only a single population to reduce heterogeneity? Do you randomize by block by bleeding type / specific drug to minimize heterogeneity?
Considerations in Selecting Patients for a Trial

- **Inclusion Criteria:** How severe should the bleeding be?
  - None (anticipation of urgent surgery), moderate to severe, or life threatening?
  - > 2g Hb or > 10% hct drop?
  - Require transfusion of > 2U blood products?
  - Should patients with ICH be included? Subdural vs intraparenchymal bleed?

- **Exclusion Criteria:**
  - No recent history of thromboembolic events that would put patient at risk of thrombosis
  - Mechanical cause such as severed vessel?