Benefit-Risk Assessment via Case Studies: Key Considerations & Best Practices

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(Acknowledgements: Qi Jiang, Amgen & Weili He, Merck)

Objective

Discuss key considerations for benefit-risk evaluation using 2 case studies
Outline

- Background and key B-R considerations for each case study:
  - Case#1: dabigatran (sub-group profiling)
  - Case#2: rivaroxaban (burden of missing data)
- Lessons learned and best practices in B-R evaluation
Case study #1:

Anticoagulant Options — Why the FDA Approved a Higher but Not a Lower Dose of Dabigatran

B. Nhi Beasley, Pharm.D., Ellis F. Unger, M.D., and Robert Temple, M.D.

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• Dabigatran is anticoagulant; approved 10/2010
• A **preventive therapy** – indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF)
• **Benefits**: prevention of strokes, heart attacks, and death
• **Risk**: bleeding
Evidence of Efficacy and Safety

Study Design: RE-LY¹

- Large, Phase III, active-controlled study in patients with AF and at least 1 additional risk factor for stroke. N=18,113 ~ 6,000/group; median fu= 2yr
- Randomized 1:1:1 to: warfarin: dabigatran-110 mg: Dabigatran-150 mg
- **Primary hypothesis**: dabigatran at either dose was non-inferior to warfarin in preventing stroke and systemic embolism.

¹RE-LY: Randomized Evaluation of Long-Term Anticoagulation Therapy (Connolly S et al NEJM, 2009) *

AF= Atrial Fibrillation.
# Evidence of Efficacy and Safety

## Efficacy and Major Safety Outcomes in RE-LY.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Dabigatran, 110 mg (N = 6015)</th>
<th>Dabigatran, 150 mg (N = 6076)</th>
<th>Warfarin (N = 6022)</th>
<th>Dabigatran, 110 mg vs. Warfarin</th>
<th>Dabigatran, 150 mg vs. Warfarin</th>
<th>Dabigatran, 150 mg vs. Dabigatran, 110 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or systemic embolism</td>
<td>183 (1.5)</td>
<td>134 (1.1)</td>
<td>202 (1.7)</td>
<td>0.90 (0.74–1.10), 0.29</td>
<td>0.65 (0.52–0.81), 0.0001</td>
<td>0.72 (0.58–0.90), 0.004</td>
</tr>
<tr>
<td>Stroke</td>
<td>171 (1.4)</td>
<td>122 (1.0)</td>
<td>186 (1.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>152 (1.3)</td>
<td>103 (0.9)</td>
<td>134 (1.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>14 (0.1)</td>
<td>12 (0.1)</td>
<td>45 (0.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncertain</td>
<td>5 (0.0)</td>
<td>7 (0.1)</td>
<td>7 (0.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>15 (0.1)</td>
<td>13 (0.1)</td>
<td>21 (0.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding episode</td>
<td>342 (2.9)</td>
<td>399 (3.3)</td>
<td>421 (3.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life-threatening bleeding episode</td>
<td>159 (1.2)</td>
<td>193 (1.5)</td>
<td>233 (1.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Data are shown for all patients with at least one event, and analyses are based on time to first event. P values are for superiority.

150 mg reduced the risk of stroke and systemic embolism more than 110 mg did but also caused more bleeding

Source: Connolly S et al., NEJM, 2009
## Overall B-R profile:

For each 1000 patients treated with dabigatran instead of Warfarin for 12 mo

<table>
<thead>
<tr>
<th>110 mg bid dose</th>
<th>150 mg bid dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefit</strong></td>
<td><strong>Benefit</strong></td>
</tr>
<tr>
<td>• 2 strokes prevented (4 fewer hemorrhagic; 2 excess ischemic)</td>
<td>• 6 strokes prevented (~3 hemorrhagic; ~3 ischemic)</td>
</tr>
<tr>
<td>• &lt; 1 systemic embolism</td>
<td>• &lt; 1 systemic embolism</td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td><strong>Risk</strong></td>
</tr>
<tr>
<td>• 7 fewer non fatal bleeds</td>
<td>• 3 fewer non fatal bleeds</td>
</tr>
<tr>
<td>• 6 fewer life threatening bleeds</td>
<td>• 4 fewer life threatening bleeds</td>
</tr>
<tr>
<td>• 5 fewer intracranial hemorrhages</td>
<td>• 4 fewer intracranial hemorrhages</td>
</tr>
</tbody>
</table>

110 mg: Non-inferior on stroke prevention, superior on bleeding  
150 mg: Superior on stroke prevention; non-inferior on bleeding

Source: Adapted from Unger EF, FDA/DIA Statistics Meeting April 13, 2011
Why FDA approved higher dose

**B-R Assessment in sub-groups**

<table>
<thead>
<tr>
<th>Elderly patients- 75 and older; N=7238</th>
<th>Patient with impaired Renal function; N=3343</th>
<th>Previous bleeding On treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>stroke</td>
<td>bleeding /1000PY</td>
<td>stroke</td>
</tr>
<tr>
<td>Dabigatran 110</td>
<td>19</td>
<td>44</td>
</tr>
<tr>
<td>Dabigatran 150</td>
<td>14</td>
<td>51</td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Lower dose: 5 extra strokes & 7 fewer bleeding
- Lower dose: 11 extra strokes & 4 fewer bleeding
- No evidence additional major bleed

- None of the sub-group population shows B-R more favorable for the lower dose
- FDA approved only the higher dose of 150mg bid.

Adapted from Unger EF, FDA/DIA Statistics Meeting April 13, 2011
### Summary of key B-R considerations

<table>
<thead>
<tr>
<th>Endpoint selection</th>
<th>Relative importance of endpoints</th>
<th>Choice of B-R metric</th>
<th>Subgroup identification</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>Clinical impact:</strong> select endpoints that are clinically important. E.g. FDA selected endpoints that represent irreversible tissue damage or death.</td>
<td>• Assigning weights is value judgment/subjective; can be informed and consensus.</td>
<td>• Consider using RR with AR for a full BRA and for good communication practices</td>
<td>• Treatment effects in subgroups of patients defined by some characteristic</td>
</tr>
<tr>
<td>• <strong>Avoid double counting:</strong> exaggerates magnitude of benefit. E.g. options: single composite, 1 efficacy and 1 safety endpoint; define new GBR score</td>
<td>• Rank endpoints in a qualitative way (stakeholder perspective vary)</td>
<td>• <strong>Metrics:</strong> E.g. Risk Difference, Excess numbers of events, NNT/NNH, Net Clinical Benefit, Exposure Adjusted Risk Analysis etc.</td>
<td>• <strong>Dabigatran:</strong> assess B-R trade-offs in vulnerable patient segments in the lower dose group.</td>
</tr>
<tr>
<td>• <strong>Value Tree/Effects Table</strong> can facilitate endpoint selection</td>
<td>• <strong>Regulator</strong>¹,²: most concerned with stroke and bleeding events that are fatal or cause irreversible harm</td>
<td></td>
<td>• <strong>Methodology:</strong> E.g. Subgroup/predictive analysis, recursive partitioning, Regression based methods, MCDA type index, simple 2x2 table etc.</td>
</tr>
<tr>
<td>• <strong>Challenges:</strong> data sources, different metrics/scales across endpoints</td>
<td>• <strong>Patient</strong>³: Substantial variation exists between patients’ willingness to tolerate bleeding risk in exchange for stroke prevention.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Input from clinical is key</td>
<td>• <strong>Wt. Elicitation:</strong> Point allocation/DCE/Swing Weight/Patient Preferences</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Case study #2:

The ATLAS ACS 2–TIMI 51 Trial and the Burden of Missing Data
(Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2–Thrombolysis In Myocardial Infarction 51)

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*Aurora and Denver, Colorado; and Los Angeles, California
Rivaroxaban is an oral anticoagulant (blood thinner) that directly and selectively inhibits factor Xa.

Previously approved for 4 clinical indications in US.

Potential benefit: reduce the risk of recurrent atherothrombotic events in patients with acute coronary syndromes.

Risk: bleeding
Evidence of Efficacy and Safety

**ATLAS ACS 2–TIMI 51:** Single pivotal Phase III double-blind, placebo-controlled trial; N=15526, max fu=31 mo

- Determine if rivaroxaban when added to standard antiplatelet therapy:
  - Is effective at reducing the risk of the composite of cardiovascular (CV) death, MI, or stroke compared with placebo in subjects with a recent ACS?

- **Primary Efficacy Endpoint** (first occurrence): Composite of CV death, MI, or stroke (including hemorrhagic).

- **Primary Safety Endpoints** (first occurrence)
  - TIMI major bleeding not associated with CABG surgery

- **Primary evaluation strategy:** *(modified intention-to-treat (mITT) analysis)*
  - randomized patients and the endpoint events that occurred after randomization and no later than the completion of the treatment phase of the study, 30 days after early permanent discontinuation of the study drug, or 30 days after randomization for patients who did not receive a study drug.
Primary Efficacy Results:
Effect of rivaroxaban on Primary Efficacy Endpoint mITT/All Strata/Combined Doses

Treatment with rivaroxaban significantly reduce the 1⁰ efficacy endpoint of death from CV causes, MI, or stroke, as compared with placebo,

Source: Burton P, Rivaroxaban, Cardiovascular and Renal Drugs Advisory Committee May 23, 2012
Primary Safety Results:

Time to First Treatment Emergent Non-CABG TIMI Major Bleeding Events TE/All Strata/Each Dose

Treatment with rivaroxaban resulted in higher rates of bleeding overall compared with Placebo in both 2.5 and 5mg bid dose

Source: Burton P, Rivaroxaban, Cardiovascular and Renal Drugs Advisory Committee May 23, 2012
Summary of key B-R considerations

.. Despite seemingly robust efficacy data, several key issues were brought up that challenge the validity of trial results......

- study design flaw
- burden of missing data
Issue with study design

1° Analysis: mITT

- events that occurred while subjects were taking study drug + 30 days after early discontinuation (OT+30d)

*FDA agreed because…*

- sponsor stated “*all efforts will be expended in capturing the status of all subjects at the end of the study.*”

**Issue:**

- Data needed for reliable ITT analyses are not available due to incomplete follow-up
…… comment by one of the ACM panelists summarized the major issue with study design…

“The decision to use mITT as the endpoint, I believe, had a profound impact here. And I think what happens when you say, the primary endpoint is 30 days after you stop study drug, is you're telling the investigators and you're telling the patients that you don't care so much about what happens later on. I think that's why they had such a large withdrawal of consent rate. I think it was preordained by the use of this so-called mITT, which is really an on-treatment analysis. And so I think it colored the trial in ways we could never recover from because we're never going to ever see the ITT data.” [ACM panelist, 2012]
Summary of key B-R considerations (contd.)

**Burden of missing data**

>15.5% prematurely discontinued (8.3% withdraw consent). Vital status not ascertained in 86% of patients who withdrew consent.

→ *serious threat to validity of the study*

# of patients with unknown vital status exceeded the total number of primary endpoint events

→ *questionable result*
The difference in the missing data nearly matched the difference in the primary outcome

→ **ample opportunity to amplify or obscure any true difference in endpoints.**

**Differential dropouts:** missing data are differential by treatment group, results biased, related to treatment efficacy or tolerability (**informative censoring**)  

→ **complicate interpretation of results.**
Decision

The sponsor company, submitted supplemental NDAs and the applications were reviewed by the FDA Cardiovascular and Renal Drugs Advisory Committee (CRDAC) on May 23, 2012 and January 16, 2014, respectively.

Each time, the company failed to gain recommendation for approval by the CRDAC.
What did we Learn?

• Recognize the importance of study design and trial conduct and impact of missing data on B–R assessment.

• Informative censoring was likely to have occurred due to the study design flaws.

• Missing data can complicate interpretation or even invalidate an otherwise important study.

• Safety signals often emerge with long-term follow-up. It is crucial to collect long-term outcome information.

• The ATLAS ACS 2–TIMI 51 trial was designed essentially as a trial using an on-treatment analysis to address the primary efficacy objective.

• For this type of trials, ITT principle should always be followed as a general rule of engagement.
Best practices

Key elements in benefit-risk evaluation

- Analysis of condition
- Unmet medical need
- Current treatment options
- Endpoint/Outcome definition
- Clinical impact/weighting considerations
- Uncertainty evaluation (study design/missing data)
- Choice of metric/Subgroup identification
- Patient preference information
- Risk evaluation and mitigation strategy

FDA BRF\textsuperscript{[9]}; CIRS-BRAT\textsuperscript{[10]}; EMA Effects Table\textsuperscript{[11]}; UMBRA\textsuperscript{[12]}

(Structured B-R Assessment)
Key References


3. FDA Briefing document, rivaroxaban, for the May 22, 2012 Meeting of the FDA/CDER Cardiovascular and Renal Drugs Advisory Committee. [link]


6. U.S. Food and Drug Administration. May 23, 2012, Meeting of the Cardiovascular and Renal Drugs Advisory Committee. Available at: [link]

7. U.S. Food and Drug Administration. January 16, 2014, Meeting of the Cardiovascular and Renal Drugs Advisory Committee. Available at: [link]


Thank you for your attention

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