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

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

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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

B-R=Benefit-Risk

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.

The NEW ENGLAND JOURNAL of MEDICINE

Case #1- Dabigatran 110mg bid vs 150mg bid

- 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-LY[1]

- 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.

[1]RE-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.*

Event	Dabigatran, 110 mg (N=6015)	Dabigatran, 150 mg (N=6076)	Warfarin (N=6022)	Dabigatran, 110 mg vs. Warfarin	Dabigatran, 150 mg vs. Warfarin	Dabigatran, 150 mg vs. Dabigatran, 110 mg
	no. of patients (% per yr)			*hazard ratio (95% confidence interval), P value*		
Stroke or systemic embolism	183 (1.5)	134 (1.1)	202 (1.7)	0.90 (0.74–1.10), 0.29	0.65 (0.52–0.81), 0.0001	0.72 (0.58–0.90), 0.004
Stroke	171 (1.4)	122 (1.0)	186 (1.6)			
Ischemic	152 (1.3)	103 (0.9)	134 (1.1)			
Hemorrhagic	14 (0.1)	12 (0.1)	45 (0.4)			
Uncertain	5 (0.0)	7 (0.1)	7 (0.1)			
Systemic embolism	15 (0.1)	13 (0.1)	21 (0.2)			
Major bleeding episode	342 (2.9)	399 (3.3)	421 (3.6)			
Life-threatening bleeding episode	159 (1.2)	193 (1.5)	233 (1.9)			

* 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

110 mg bid dose	150 mg bid dose
Benefit • 2 strokes prevented (4 fewer hemorrhagic; 2 excess ischemic) • < 1 systemic embolism Risk • 7 fewer non fatal bleeds • 6 fewer life threatening bleeds • 5 fewer intracranial hemorrhages	Benefit • 6 strokes prevented (~3 hemorrhagic; ~3 ischemic) • < 1 systemic embolism Risk • 3 fewer non fatal bleeds • 4 fewer life threatening bleeds • 4 fewer intracranial hemorrhages

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-

Elderly patients- 75 and older; N=7238

	stroke /1000PY	bleeding /1000PY
Dabigatran 110	19	44
Dabigatran 150	14	51

- Lower dose: 5 extra strokes & 7 fewer bleeding

Patient with impaired Renal function; N=3343

	stroke /1000PY	bleeding /1000PY
Dabigatran 110	24	57
Dabigatran 150	13	53

- Lower dose: 11 extra strokes & 4 fewer bleeding

Previous bleeding On treatment

Dabigatran 110	16%
Dabigatran 150	14%
Warfarin	12%

- 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

Endpoint selection	Relative importance of endpoints	Choice of B-R metric	Subgroup identification
• [1]Clinical impact: select endpoints that are clinically important. e.g. FDA selected endpts that represent irreversible tissue damage or death. • Avoid double counting: → exaggerated magnitude of benefit. e.g options: single composite; 1 efficacy and 1safety endpoint; define new GBR score • Value Tree/Effects Table can facilitate endpoint selection • Challenges: data sources, different metrics/scales across endpoints • Input from clinical is key	• Assigning weights is value judgment/subjective; can be informed and consensus. • Rank endpoints in a qualitative way (stakeholder perspective vary) • Regulator[1,5,]: most concerned with stroke and bleeding events that are fatal or cause irreversible harm • Patient[13]: Substantial variation exists between patients' willingness to tolerate bleeding risk in exchange for stroke prevention. • Wt. Elicitation: Point allocation/DCE/Swing Weight/Patient Preferences	• Consider using RR with AR for a full BRA and for good communication practices • Metrics : *e.g. Risk Difference, Excess numbers of events, NNT/NNH, Net Clinical Benefit, Exposure Adjusted Risk Analysis* etc.	• Treatment effects in sub-groups of patients defined by some characteristic • Dabigatran: assess B-R trade-offs in vulnerable patient segments in the lower dose group. • Methodology: e.g. Sub-group/predictive analysis, recursive partitioning, Regression based methods, MCDA type index, simple 2x2 table etc.

RR= Relative Risk; AR= Absolute Risk; BRA=Benefit-Risk assessment

Case study #2:

VIEWPOINT

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)

Mori J. Krantz, MD,*†‡ Sanjay Kaul, MD§‖

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Case #2: Rivaroxaban in ACS

- 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 athero-thrombotic events in patients with acute coronary syndromes.
- *Risk*: bleeding

Xarelto (rivaroxaban)

ACS= Acute Coronary Syndrome

Evidence of Efficacy and Safety

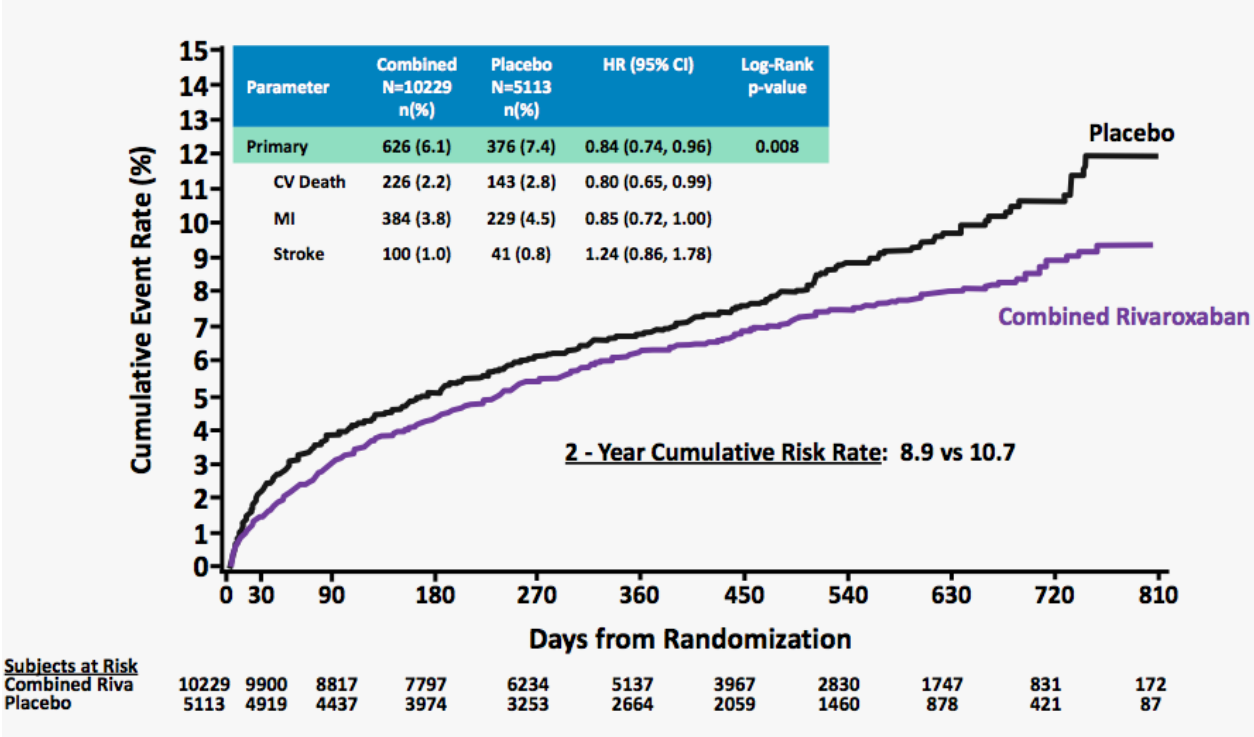
ATLAS ACS 2–TIMI 51: Single pivotal Phase III double-blind, placebo-controlled trial; N=15526, max fu=31 mo

- 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.

ATLAS ACS 2–TIMI 51 = 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)

Primary Efficacy Results:

Effect of rivaroxaban on Primary Efficacy Endpoint mITT/All Strata/Combined Doses

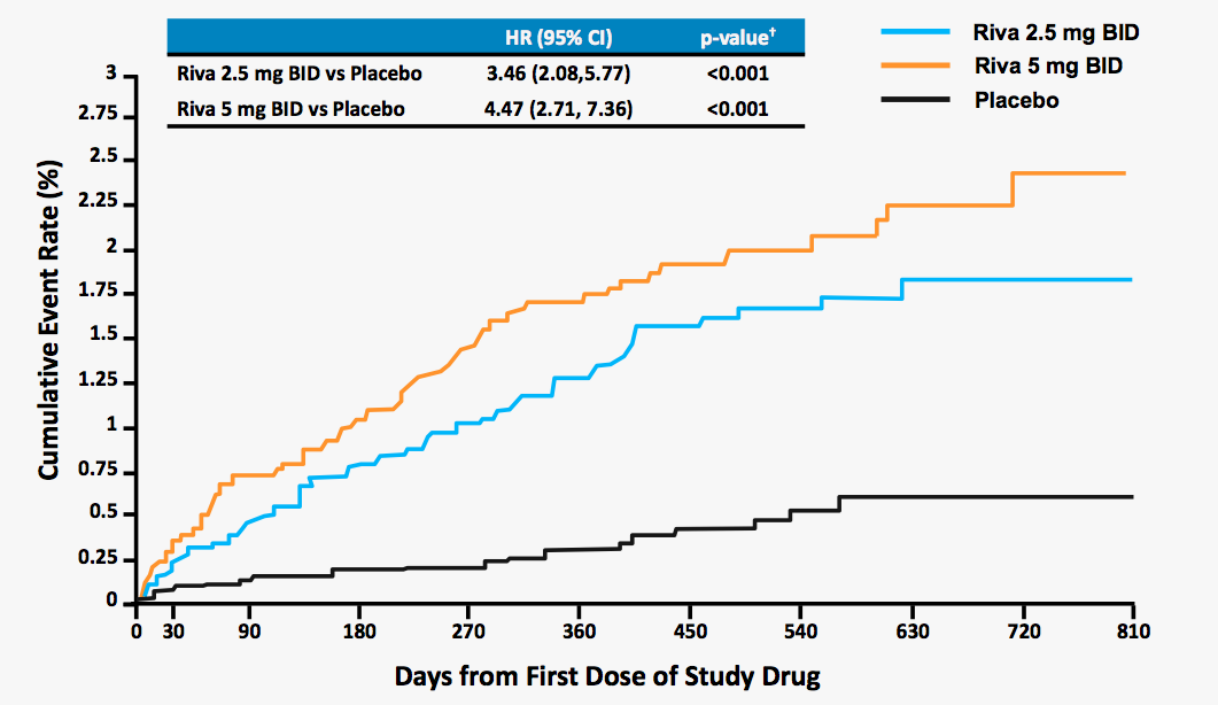


Treatment with rivaroxaban significantly reduce the 1º efficacy endpoint of death from CV causes, MI, or stroke, as compared with placebo,

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

Summary of key B–R considerations (contd.)

Issue with study design

1º 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

Summary of key B–R considerations (contd.)

…… 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]

ACM=Advisory Committee Member

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*

Summary of key B–R Considerations (contd.)

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.

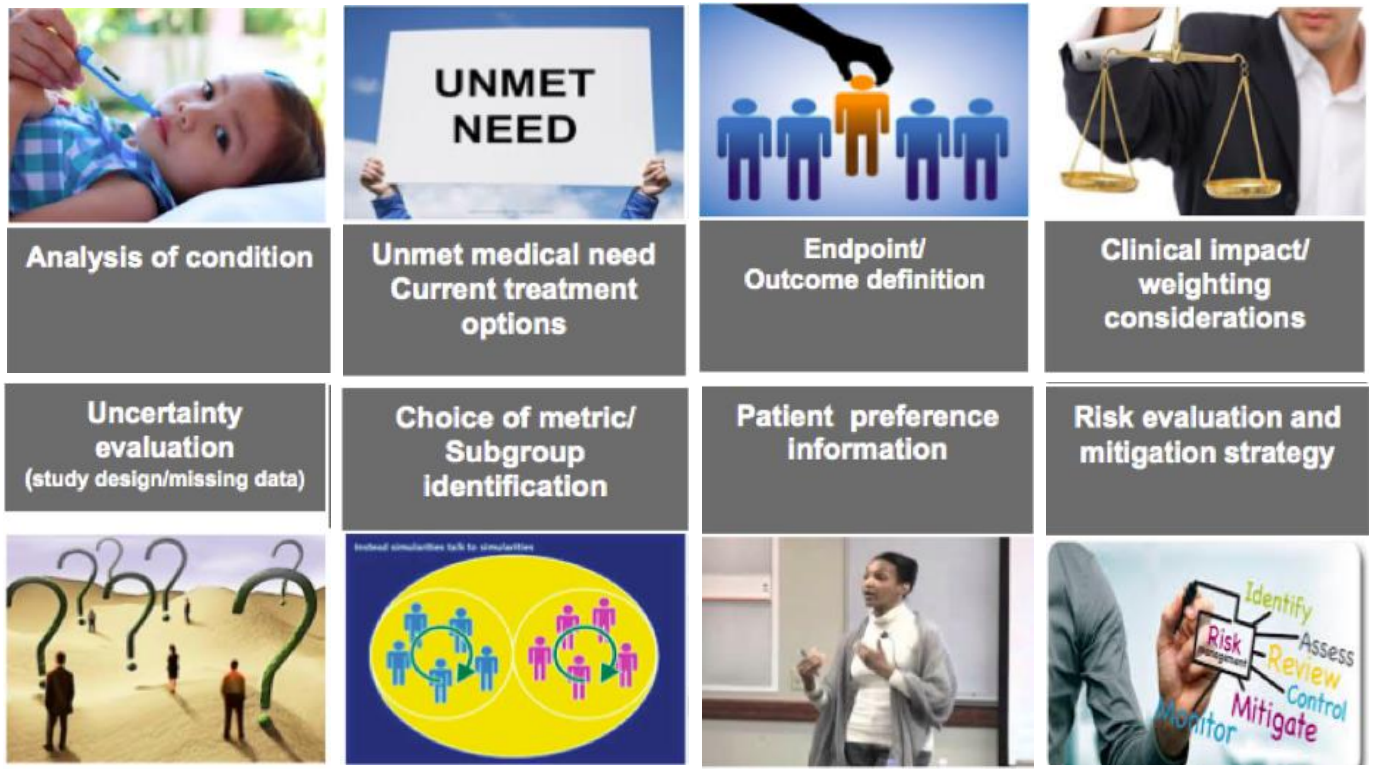
Each time, the company failed to gain recommendation for approval by the CRDAC.

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



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

(Structured B-R Assessment)

BRF=Benefit-risk framework; CIRS= Center for Innovation in Regulatory Science; BRAT=Benefit-Risk Action Team; Universal Measures for Benefit-risk Assessment

Key References

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Thank you for your attention

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