Using PK/PD to inform NOAC dosing: Should we consider pharmacometric-guided dosing of NOAC agents to maximize the benefit: risk relationship?

An Industry Perspective

Paul A Reilly, PhD
Clinical Research, Boehringer Ingelheim, Inc

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Do We Need to Monitor NOACs to Improve Benefit-Risk?

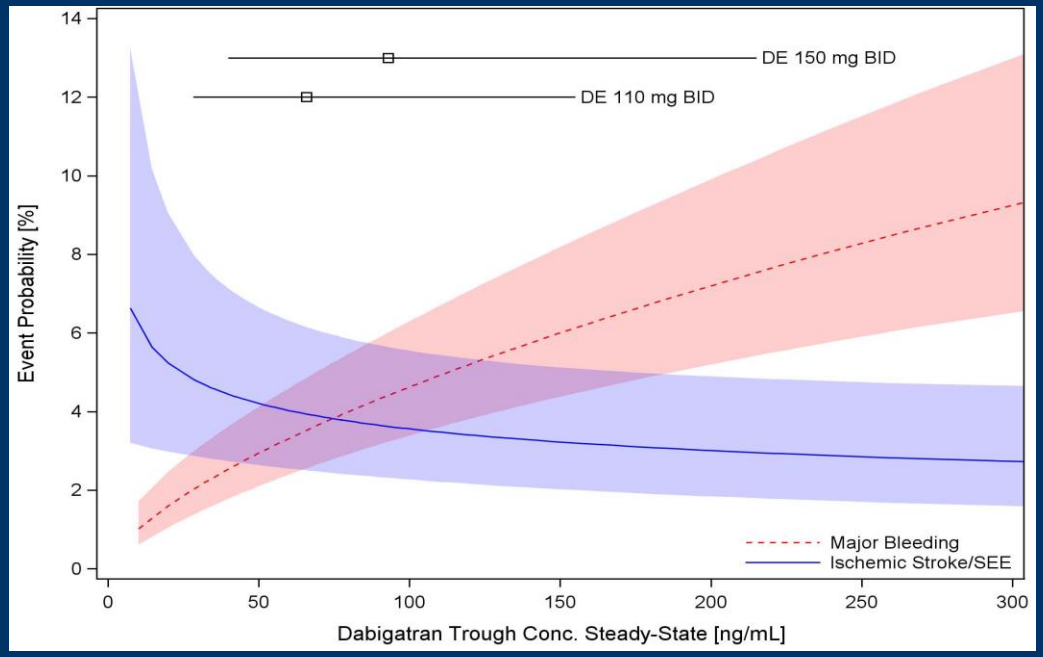
- Novel Oral Anticoagulants (NOACs) were developed as fixed dose drugs with no need for monitoring
  - NOACs are safe and effective, when used in accordance with approved label based on outcomes data from >50,000 patients

- Can you improve the benefit-risk by individual dosing based on biomarkers?

What are the challenges?

Exposure-Response in RE-LY:

what is not self-evident



Reilly PA, et al. *J Am Coll Cardiol* 2014; 63: 2885 6

- Patient demographics are different at different concentrations
- Adjusting exposure to change event frequency always has a cost →what is the Net Clinical Benefit?

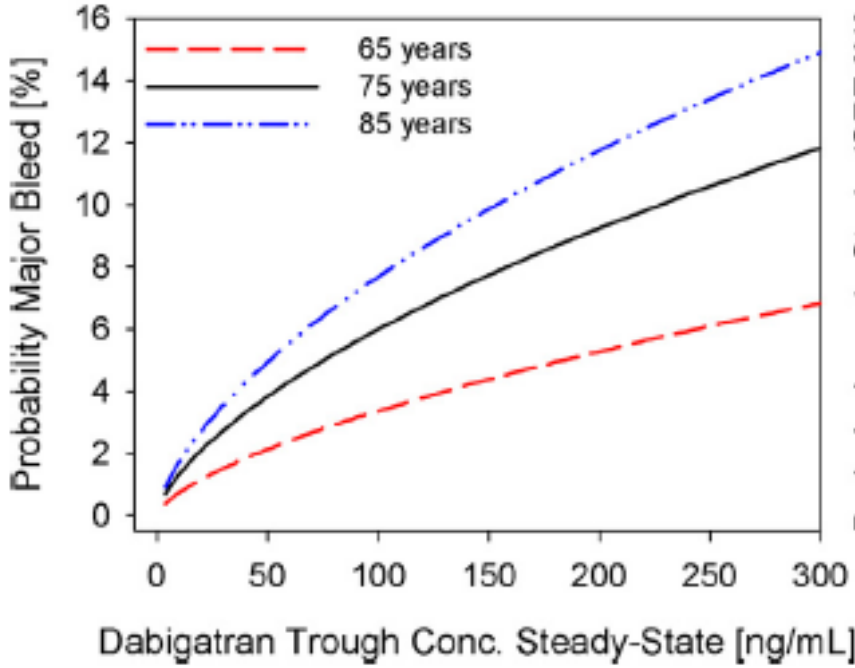
- The event rates do not apply to the whole RE-LY population (72 yo male, prior stroke, diabetes)

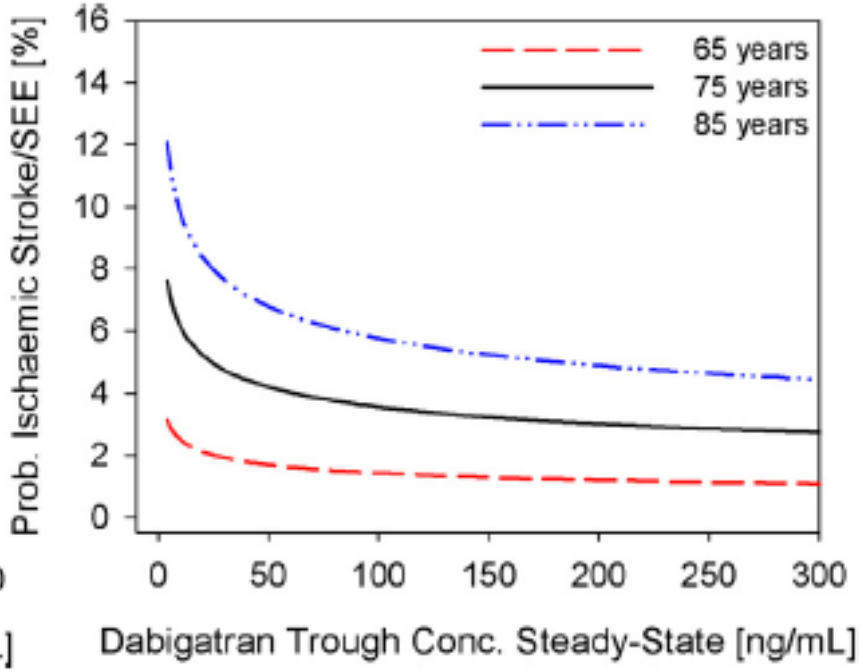
Dose Adjustment: A yet-to-be-defined target

- A therapeutic range for each NOAC may be difficult to identify, there are hidden assumptions
  - Is it an arbitrary definition based on distribution of plasma levels, biomarkers or clinical outcomes?

- Is a target range for all patients or is it specific to the type of patient?
  - e.g. concomitant medications, elderly (age>80), prior stroke, renal dysfunction

Risk Varies by Patient Demographics





Reilly PA, et al. *J Am Coll Cardiol* 2014; 63: 2885-6

Major bleeding event (left) and ischemic stroke/systemic embolic event (right) versus trough dabigatran plasma concentration in atrial fibrillation patients by age (65, 75, and 85 years). Covariates: sex, prior stroke, diabetes.

Clinical characteristics (e.g. age and renal function) are at least as, if not more important, compared to plasma levels to determine risk of clinical outcomes: the optimal drug level may differ by patient subgroup.

The Problem with Measuring: Is there a reliable and approved assay for each NOAC?

- Apixaban, rivaroxaban, edoxaban, betrixaban
  - Anti-Xa assay, PT for rivaroxaban?
  - Anti-Xa not yet widely available

- Dabigatran
  - ECT, dTT, aPTT, TT
  - ECT not widely available, dTT not approved for clinical use in USA, aPTT variability in methods and correlation, TT methods variability

Each NOAC Would Need to Define the Dose Algorithm: What are the currently available doses in USA?

Approved doses may be limited to specific kinds of patients or indications

- Dabigatran 75, 150 bid,
- Rivaroxaban 10, 15, 20 mg qd
- Apixaban 5, 2.5 mg bid
- Edoxaban 15, 30, 60 mg qd

Posology

- E.g.150 bid down-titrated to 150 qd
  - Peak trough ratios of 2:1 vs. 6:1

Unforseen impact on stroke/bleed frequency?

Measure the Results: can every candidate patient be titrated successfully?

Target based on biomarker

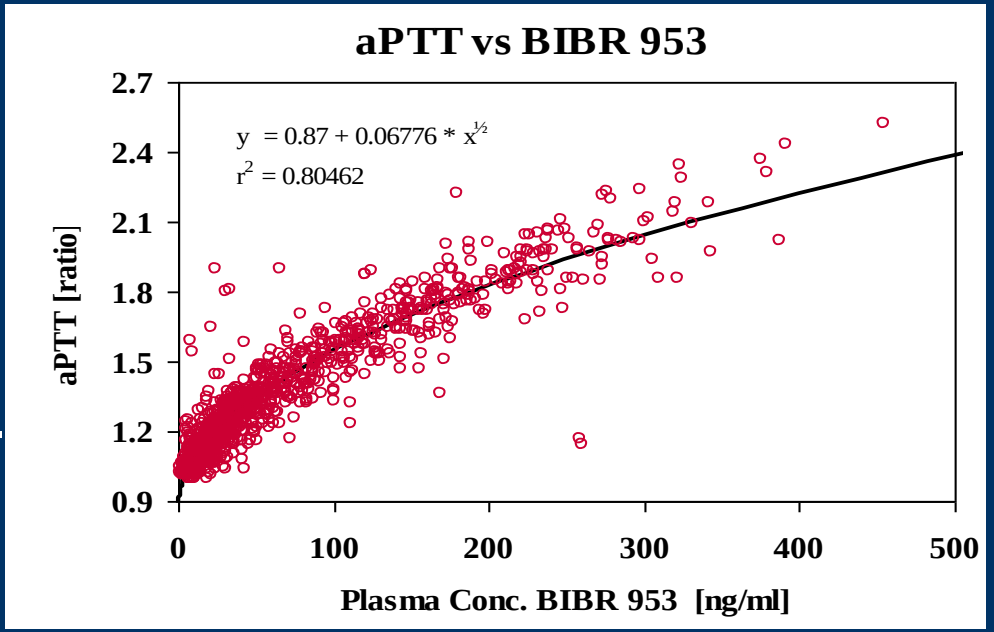
- Target Range hit → OK
  - Re-test? months, years, clinical event
- Target range missed → Re-test, different dose?
  - What proportion of failures?

Biomarker vs. clinical outcome

- What is the patient benefit of achieving the biomarker target?

Biomarkers have Limitations: Sources of Variability

- Biomarker test accuracy and sensitivity
- Test interference
- Intra-individual variability
- Peak-trough variability
  →time of measurement vs. time of dose



Level of Evidence for Adjusted Dose NOACs: we need evidence beyond a biomarker

What benefit do we wish to achieve with adjusted dosing of NOACs?

- 20% decrease in bleeding?
- 20% decrease in ischemic stroke?

Cost of bleeding benefit

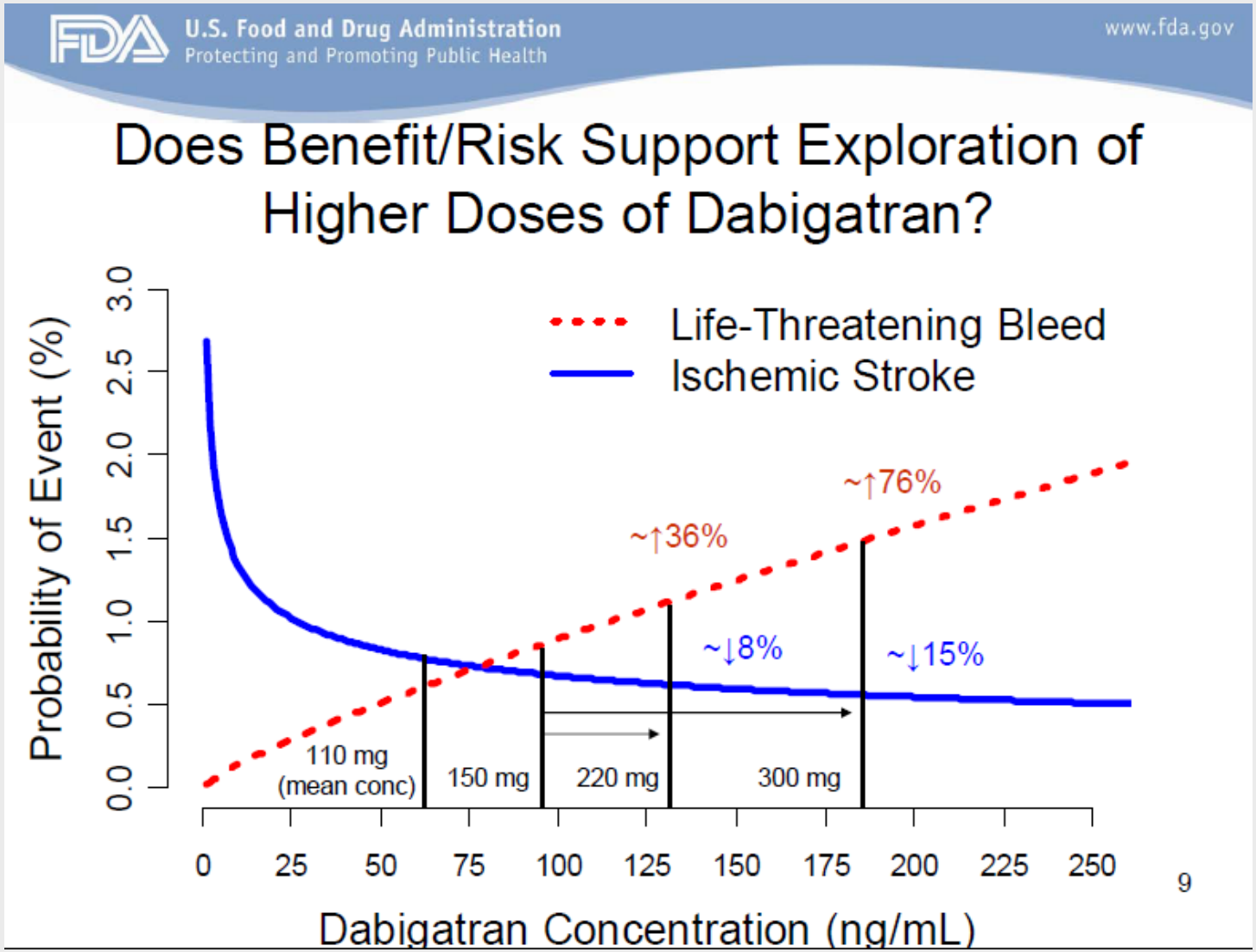
- 5% ↑ in ischemic stroke?

Cost of ischemic stroke benefit

- 10% increase in major bleeding?

Net Clinical Benefit calculation!

FDA analysis : Dabigatran Advisory Committee Meeting 20 Sept 2010



Level of Evidence

Can we guide clinicians to implement adjusted dose NOACs based on biomarker data alone ?

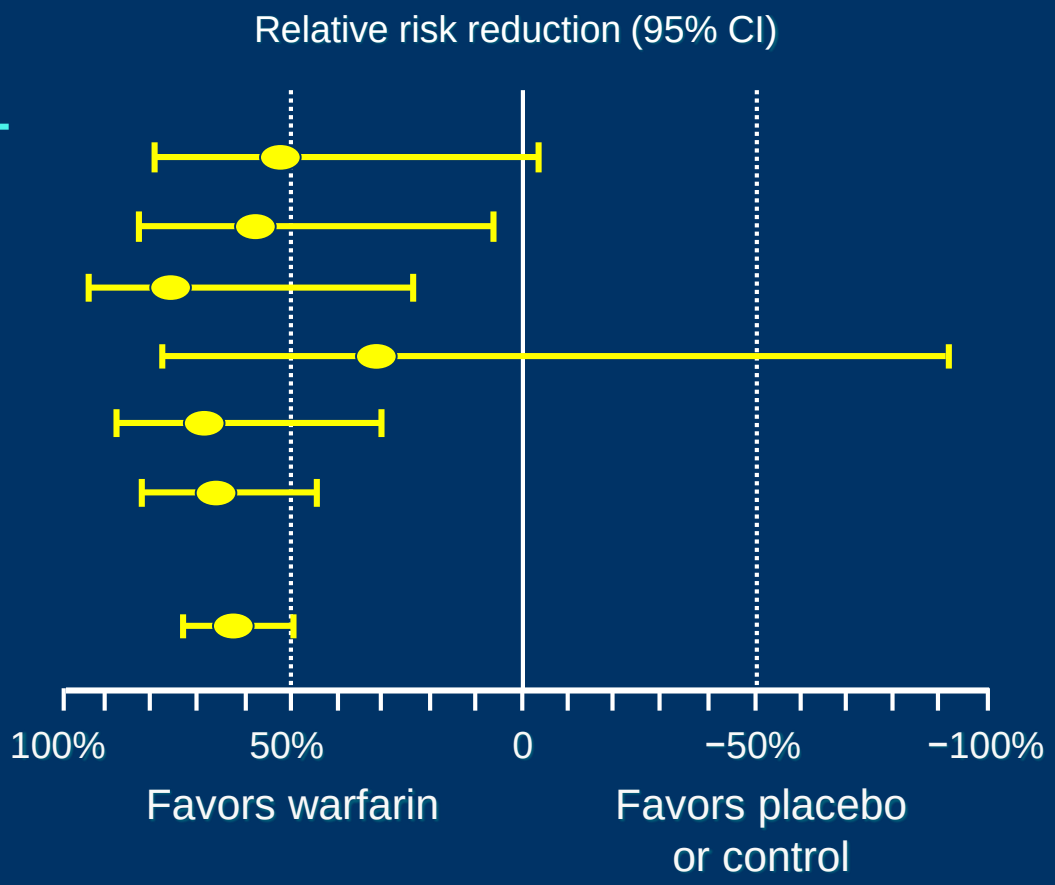
- Introduce a new dose algorithm without safety or efficacy data?
- Usage of biomarkers to target clinical benefit may require a device exemption or submission

Are you able to do a randomized controlled clinical trial? What would it look like?

  - fixed dose vs. adjusted dosing with 20% benefit in bleeds/ischemic events and no more than x% increase in complementary endpoint (or NCB endpoint)

After years of fixed dose, mini-dose, +/- ASA, lower INR range, the efficacy of adjusted dose warfarin is supported by clinical outcome data

Study	Year
AFASAK I	1989; 1990
SPAF I	1991
BAATAF	1990
CAFA	1991
SPINAF	1992
EAFT	1993
All trials *(n 6)*	
N 2,900	



Hart RG, et al. *Ann Intern Med*. 2007;146:857-867.

Conclusions

There are several challenges in trying to implement adjusted dose NOACs:

- The target levels (therapeutic range) for each NOAC and each risk profile would need to be defined
- Optimize for bleeds or strokes or both?
- Fluctuations within patients, frequency of adjustments
- Methodological limitations

Other Considerations

- NOACs do not fulfill the criteria for a drug with a narrow therapeutic range
- Dosing based on patient demographics may be as good as adjusted dose monitoring
- Any assumed improvement in NOAC benefit-risk should not be based on biomarker data alone, there should be clinical outcomes supporting safety and efficacy
- No supportive data from a randomized controlled trial of fixed dose vs. adjusted dose are available