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

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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

- 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)

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

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

Unforeseen impact on stroke/bleed frequency?
Measure the Results: can every candidate patient be titrated successfully?

Target based on biomarker

• Target Range hit $\rightarrow$ OK
  – Re-test? months, years, clinical event

• Target range missed $\rightarrow$ 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

\[ y = 0.87 + 0.06776 \times x^{0.5} \]
\[ r^2 = 0.80462 \]
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!
Does Benefit/Risk Support Exploration of
Higher Doses of Dabigatran?

- Life-Threatening Bleed
- Ischemic Stroke

Probability of Event (%)

Dabigatran Concentration (ng/mL)
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

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All trials \((n = 6)\)

\(N = 2,900\)

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