Can we do better at preventing strokes and avoiding bleeding? Some thoughts about regulatory requirements for greater personalization of NOAC dosing

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Background

- There are robust data on the relationship between drug concentrations and clinical outcomes for two of the four approved NOACs: dabigatran and edoxaban
- PK/PD modeling data suggest that some patients are currently being treated with doses that are either too low or too high, increasing the risks for ischemic stroke or bleeding, respectively
- Factor-based dosing or therapeutic drug monitoring probably would result in better therapeutic outcomes than those obtained with the fixed dose regimens studied in the Phase 3 clinical trials

Do we need outcomes studies of personalized dosing regimens?

Assumptions:

1) We understand the drug concentration-outcome relationships for efficacy and safety
2) We are able to determine a target range of drug concentrations that best balances the benefits and risks of the drug, based on 1)
3) We understand the pharmacokinetic characteristics of the drug

The answer depends on the whether the proposed personalized dose is within, below or above the range of doses for which we have reliable outcomes

Do we need outcomes studies of personalized dosing regimens?

- Scenario 1: The personalized dose is expected to result in drug concentrations in the target range and is either within or below the range of doses for which we have reliable outcomes data: **Probably not**
  - Labeling frequently recommends use of unstudied doses that are between or less than studied doses to account for such factors as renal impairment or inhibition of a drug-metabolizing enzyme

Do we need outcomes studies of personalized dosing regimens?

- Scenario 2: The personalized dose is expected to result in drug concentrations in the target range and is above the range of doses for which we have reliable outcomes data: **Sometimes**
  - Labeling occasionally recommends use of an unstudied dose that is above the range of studied doses to account for concomitant use with an inducer of a drug-metabolizing enzyme that results in reduced blood concentrations of the drug

Do we need outcomes studies of personalized dosing regimens?

- Scenario 2: The personalized dose is expected to result in drug concentrations in the target range and is above the range of doses for which we have reliable outcomes data: **Sometimes**
  - Factors militating for an outcomes study:
    - Concern about local effects of the drug (i.e., GI bleeding)
    - Risk of catastrophic outcomes with unexpectedly high drug concentrations

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