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A Model and Systems Based Approach to Safety and Efficacy Questions Related to Generic Substitution - A Novel Oral Anticoagulants Case Study

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Bioavailability (BA) and Bioequivalence (BE) defined by the FDA

- **BA** is defined as **the rate and extent** to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.
- **BE** serves as a surrogate of therapeutic equivalence and relies on blood/plasma based pharmacokinetic (PK) measures such as **AUC and C_{max}** that are reflective of systemic exposure.
- **Standard BE limits**: the 90% confidence interval for the test/reference ratio of AUC and C_{max} must lie within **80-125%**.

PURPOSE

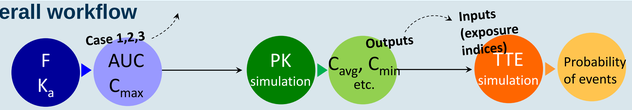
- The objective of this collaborative research was to determine **the impact of hypothetical bio-IN-equivalence (BIN) on the efficacy and safety profiles** of the novel oral anticoagulants (**NOACs**): dabigatran, edoxaban, rivaroxaban, and apixaban.

METHODS

- To determine **the impact of BIN** in AUC and/or C_{max} on **the probability of experiencing an ischemic stroke (efficacy) or a major bleeding event (safety)**, we simulated out **3 sets of BIN scenarios by altering the rate (k_a) and/or extent (F)** at which the drug is absorbed from its product.
- Resulting changes in PK were then implemented into population pharmacokinetic/pharmacodynamic (**pop-PK/PD**) and time to event (**TTE**) models available for the NOACs from their respective New Drug Applications (NDAs) and the literature.
- **Comparison with real-world data:** additional statistical analyses were performed to compare the results to the real-world data from FDA Adverse Event Reporting System (FAERS) and Truven MarketScan Health Analytics.
- **Study cases**

Case	BE in C_{max}	BE in AUC	Bio-IN-equivalence in
1	**No**	**No**	**C_{max} & AUC**
2	**No**	Yes	**C_{max}**
3	Yes	**No**	**AUC**
4	Yes	Yes	-

- **Overall workflow**

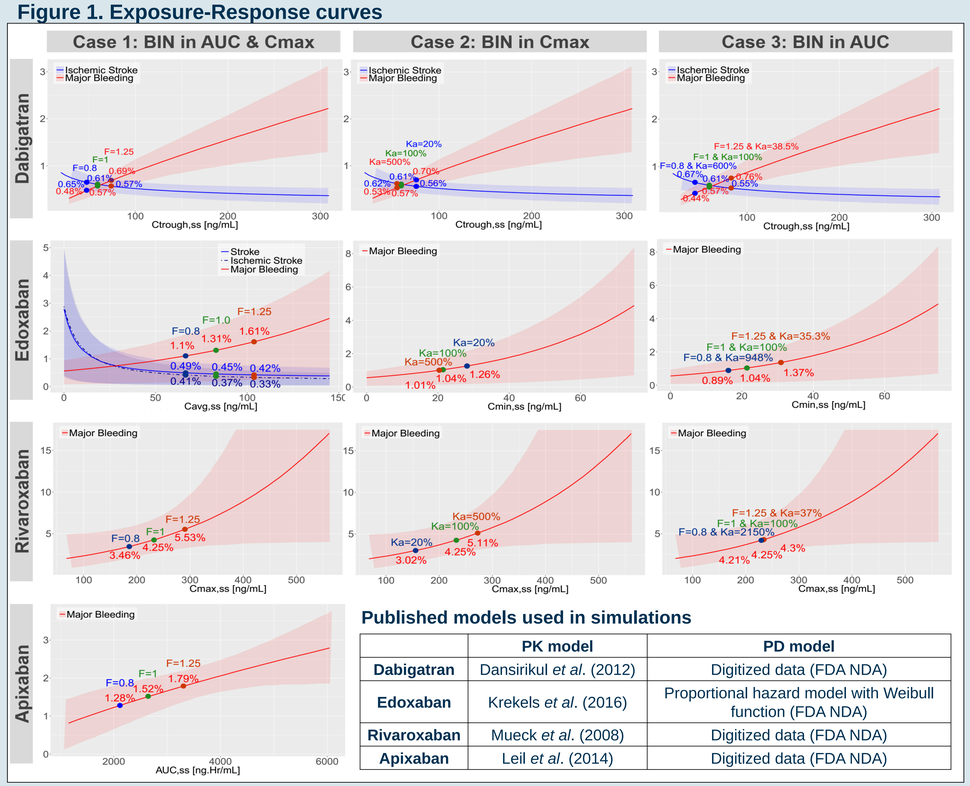


- **Software**
  - R (version 3.4.0): pre- and post- processing of data and visualizations
  - NONMEM® (version 7.3): pop-PK and TTE simulations
  - WebPlotDigitizer (version 3.12): digitizing exposure-response (ER) curves

RESULTS

- The changes in number of stroke events of edoxaban and dabigatran are 5-fold and ~2-fold lower respectively, than those of bleeding events. → These findings show that **the impact of BIN is high on bleeding events with steeper exposure-response (ER) curves** compared to stroke events that have more shallow ER curves.
- We did not test the impact of BIN on efficacy of apixaban and rivaroxaban as there is a shallow ER relationship for these drugs in the FDA reports.
- The ER curves from the FDA reports were established using **different PK inputs**: C_{max} for rivaroxaban, AUC_{ss} for apixaban, C_{avg} and C_{min} for edoxaban, and C_{trough} for dabigatran. Therefore, **computed probabilities provide trends** but cannot be directly compared to one another.

Figure 1. Exposure-Response curves



Published models used in simulations

	PK model	PD model
Dabigatran	Dansirikul *et al*. (2012)	Digitized data (FDA NDA)
Edoxaban	Krekels *et al*. (2016)	Proportional hazard model with Weibull function (FDA NDA)
Rivaroxaban	Mueck *et al*. (2008)	Digitized data (FDA NDA)
Apixaban	Leil *et al*. (2014)	Digitized data (FDA NDA)

Figure 2. Comparison of risk probabilities

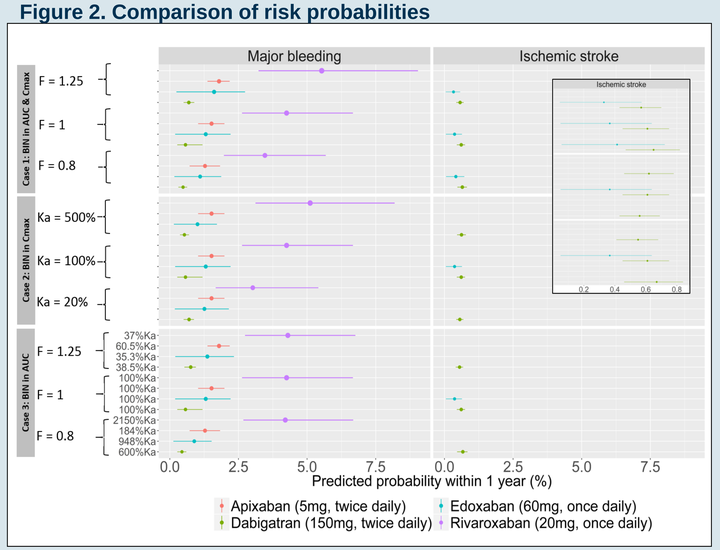
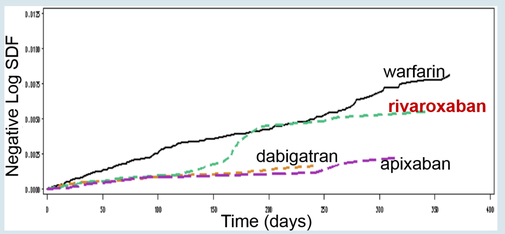


Figure 3. Real-world data: survival curves for overall major bleeding in different treatment group



CONCLUSIONS

- Changes in absorption and PK of NOACs as a result of BIN have **a greater impact on the probability of experiencing a major bleeding event** than the probability of experiencing an ischemic stroke within 1 year.
- **Future work** has to be conducted in order to **harmonize employed PK/PD indices across NOACs**, which would allow for a direct comparison of efficacy and safety predictions.

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