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An Idea for a Mid to Long Term Strategy for Pradaxa

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Background – Experience after the Pradaxa SPAF Launch

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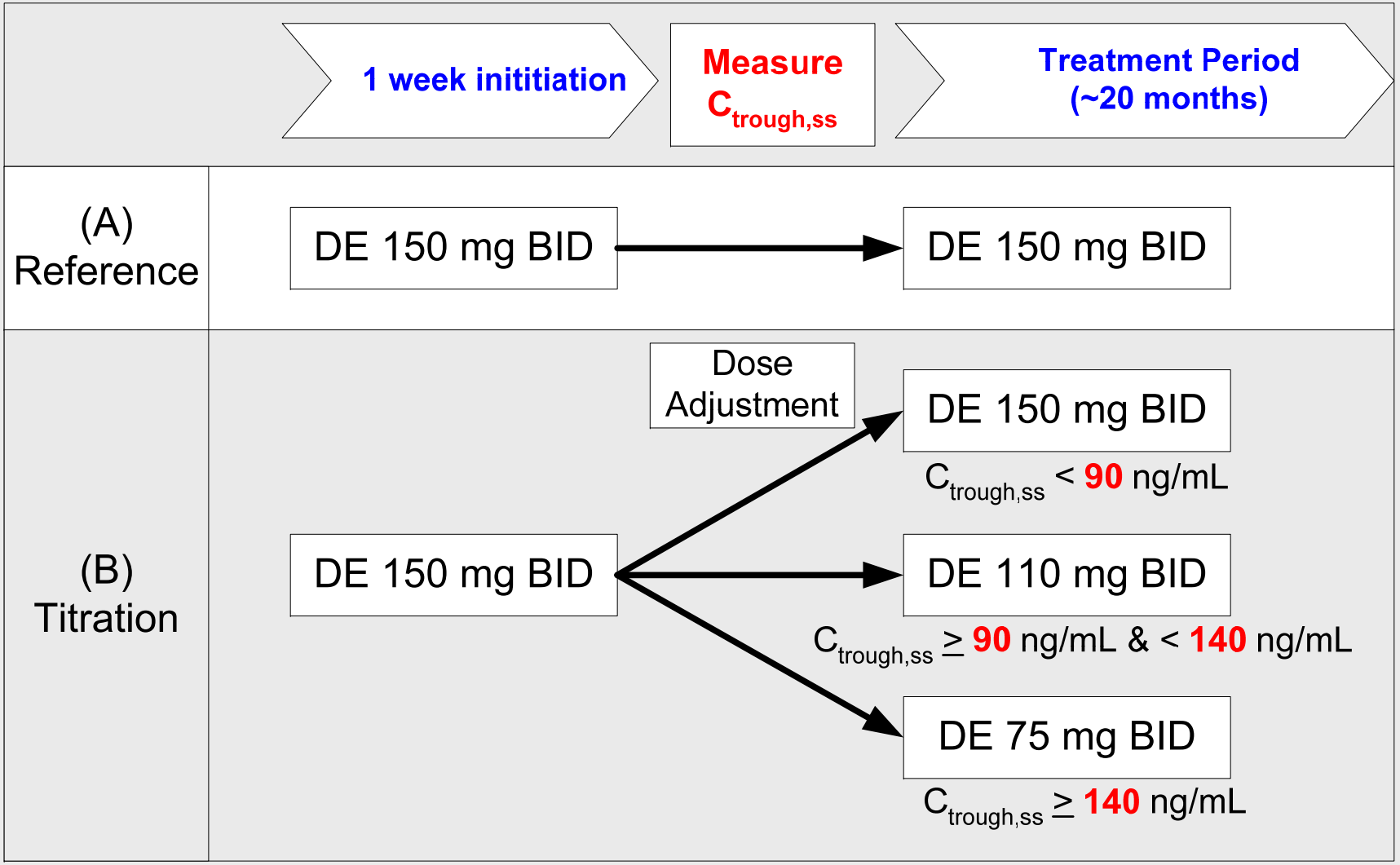
- Patients on older OACs are accustomed to and many appear to like and expect frequent interactions with the Health Care system and its staff
- Switches from older OACs to NOACs are uncommon in the marketplace
- Most new AF patients still are prescribed an older OAC
- Prescribers often want to know the extent of anticoagulation each patient is receiving via their current anticoagulant
- External experts and the media have expressed concerns about a “one size fits all” OAC, since dose adjusted OACs may have optimized outcomes
- Xarelto competes effectively against Pradaxa despite inferior ROCKET data
- Eliquis is perceived to have the best outcomes data of all NOACs
- FDA has indicated that only path towards approval of 110 mg dose would be Modeling & Simulation results followed by a PK/PD study

Modeling % Simulation – „Study“ Design



Results
Distribution of Doses and Exposure

Distribution of Dabigatran Doses

Dabigatran Dose	(A) Reference	(B) Titration
75 mg bid	---	25.5%
110 mg bid	---	29.9%
150 mg bid	100%	44.6%

- Majority of patients eligible for 150 mg bid
- Significant amount assigned to 75 mg bid

Distribution of Dabigatran Expos

N=5000	Ctrough,ss Median	Ctrough,ss P10 – P90
(A) Reference	**97.1**	48.6 – 199.4
(B) Titration	**77.0**	48.6 – 101.6

- Shift in exposure
- Median Ctrough,ss ~21% reduced
- Minimum exposure levels maintained
- 90th percentile significantly reduced

Results
Model Predicted Outcome

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Absolute Event Rates, not annualized

	Ischemic Stroke/SEE		Major Bleeding	
	Mean*	90% CI[$]	**Mean***	90% CI[$]
(A) Reference	**1.26**	1.01 – 1.55	**4.38**	3.91 – 4.89
(B) Titration	**1.34**	1.08 – 1.63	**3.49**	3.08 – 3.96

*risk of event within median RE-LY duration [~20 months], not annualized;
[$] Clopper-Pearson (Exact); [§]Range: 10th percentile – 90th percentile

Relative Risk

(B) Titration vs. (A) Reference	**Rel. Risk**	90% CI
Ischemic Stroke/SEE	**1.06**	(0.76 – 1.50)
Major Bleeding	**0.80**	(0.66 – 0.97)

Titration vs. Reference

- Risk of ischemic stroke/SEE events comparable (Relative Risk 1.06)
- Risk of major bleeding events significantly reduced (Relative Risk 0.8)

Results
Comparison to Warfarin (observed RE-LY data)

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Absolute Event Rates, not annualized

	Ischemic Stroke/SEE		Major Bleeding	
	Mean*	90% CI[$]	**Mean***	90% CI[$]
(B) Titration (n=5000)	**1.34**	1.08 – 1.63	**3.49**	3.08 – 3.96
(C) Warfarin (n=4597)	**1.68**	1.38 - 2.02	**5.83**	5.27 - 6.43

*risk of event within median RE-LY duration [~20 months], not annualized;
[$] Clopper-Pearson (Exact); [§]Range: 10th percentile – 90th percentile

Relative Risk

(B) Titration vs. (C) Warfarin	**Rel. Risk**	90% CI
Ischemic Stroke/SEE	**0.80**	(0.58 – 1.11)
Major Bleeding	**0.60**	(0.50 – 0.72)

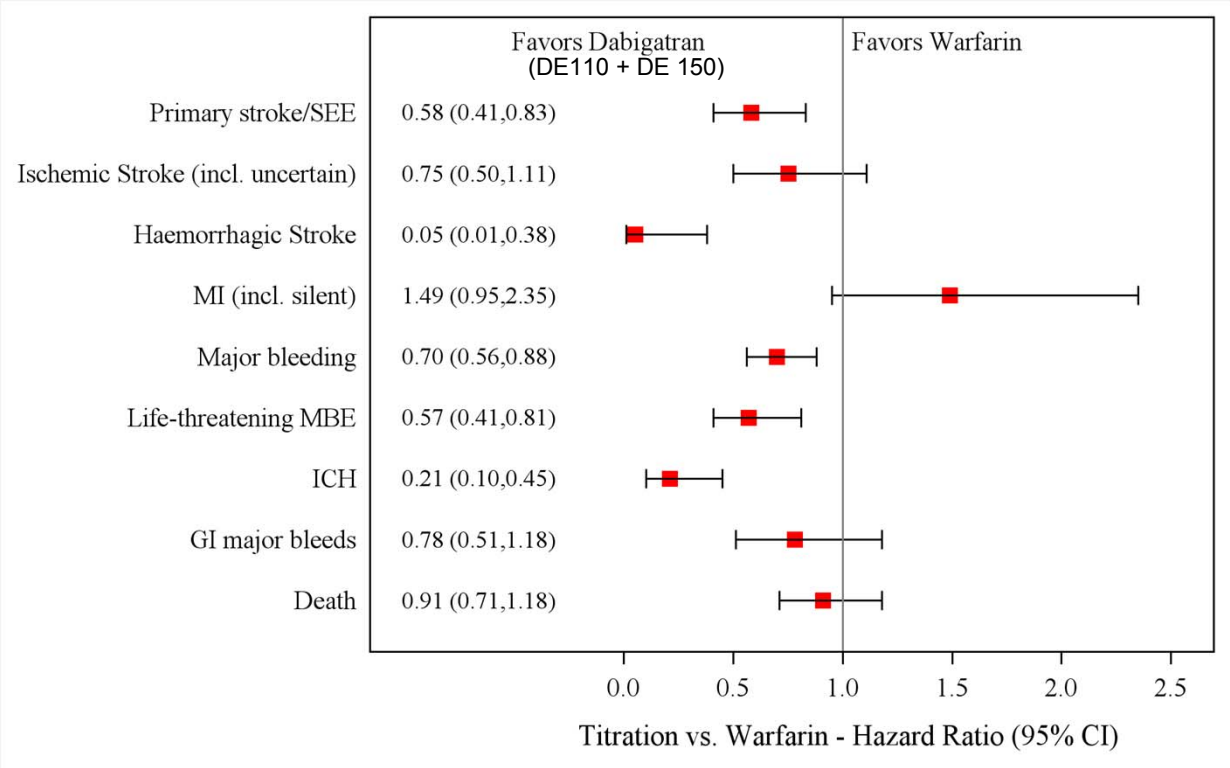
Titration vs. Warfarin

- Only RE-LY warfarin patients from centers that contributed PK measurements were considered (center matching)
- Risk of ischemic stroke/SEE events reduced (Relative Risk 0.8)
- Risk of major bleeding events significantly reduced (Relative Risk 0.6)
- Comparison needs to be handled with care. A potential bias can not be excluded due to the type of analysis.

Impact of Dabigatran Dose Adjustment on Clinical Outcome in AF Patients

COMPARISON OF OBSERVED DABIGATRAN VS. OBSERVED WARFARIN OUTCOMES FROM RE-LY

Results – Clinical Outcome
"Dabigatran Titration vs Warfarin" – Safety Dataset

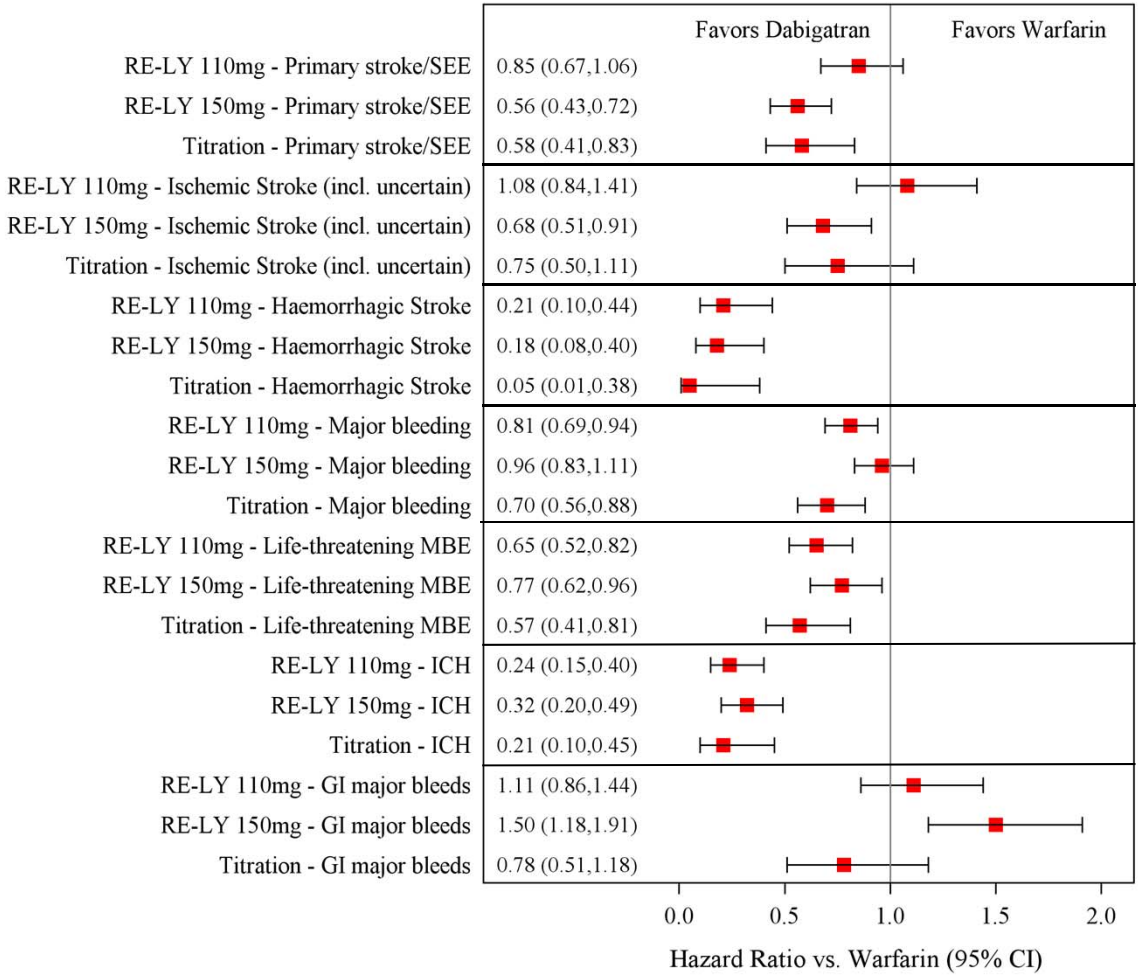


Number of patients

Treatment	Titration
DE 110 mg	1081
DE 150 mg	2005
Warfarin	3961
Total	**7047**

Optimally treated (=titrated) dabigatran patients reveal a promising efficacy and safety profile compared to matched warfarin group.

Results – Clinical Outcome
"Titration vs RE-LY" – Safety Dataset



Number of patients

Treatment	Titration	RE-LY
DE 110 mg	1081	5983
DE 150 mg	2005	6059
Warfarin	3961	5998
Total	**7047**	**18040**

Titration patients have an efficacy profile that is comparable to the RE-LY DE 150 mg group and a safety profile that is comparable to the RE-LY DE 110 mg group

Potential Mid to Long Term Strategy

- Discuss Modeling & Simulation data with FDA and explore potential path forward to approval of such an approach:
  - PK/PD study only acceptable?
  - Trial with bleeding endpoints required?
  - “Real world trial” using electronic health records of titration strategy as alternative? (e.g. within regulated system such as KP which would be more feasible than “RE-LY 2” from a budget and timeline perspective)
- Explore timing of such results compared to that of (1) globally available lab test, (2) a point of care testing device, and (3) the Pradaxa antidote

➔ If data acceptable to regulators: Re-Launch Pradaxa with titration strategy (resulting in significantly fewer strokes and significantly fewer bleeding events compared to warfarin), Point of Care testing device and availability of Antidote

Open Questions

- Would we exclude patients from Pradaxa use in AF because of insufficient exposure?
- If yes, which percentage of the overall population would be excluded?
- Given a ≈40% intra-individual variability of DE concentrations, can a simple titration regimen be designed with a low need for multiple titrations?
- Will some of the assumptions change over time with more familiarity in the Marketplace on NOACs without the need for titration?
- Which extent of new data would be needed to reflect a titration strategy in the label (including differences between countries)?
- Would this strategy endanger the superiority label vs. warfarin?
- What would be the implication of such a strategy for indications other than SPAF?

Potential Mid to Long Term Strategy - Alternative

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- BI has been approached by Astra Zeneca about a potential co-development and co-promotion of their Direct Thrombin Inhibitor which is about to enter Phase III
- The AZ approach (received after the titration idea was developed at BI) is very similar to the aforementioned potential BI strategy:
  - Titration of dose, e.g. one week after first dosing
  - Have specific lab test available at time of launch
  - Have reversal agent available at time of launch
  - AZ DTI is expected to be a once-daily therapy with low peak to trough ratio (exposure testing potentially independent of timing of last dose) and low intra-individual variability

Proposed Concrete Next Steps

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1. Prepare meeting request and discuss Modeling data as well as potential PK/PD study with FDA
2. Conduct Market Research to test potential acceptance of titration strategy in Marketplace
3. Develop models assessing cost sensitivity to payers under different assumptions
4. Conduct Challenge Meeting to further define Pros and Cons of titration strategy including MAPOR, Regulatory, Marketing, Medicine, IPM, etc.
5. Have VC with Astra Zeneca after US label of apixaban is available to further exchange thoughts on a potential collaboration