The Role of Pharmacokinetic and Pharmacodynamic Measurements in the Use of Direct Oral Anticoagulants

Future Perspectives

How to better use the available data
How to fill the gaps in our knowledge about PK/PD
Future ways on how knowledge can be obtained

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Use of Dabigatran

in the overall population

in subgroups of patients at particular risk of bleeding

in patients with an acute event such as major bleeding or acute surgery

How can clinical decision making be optimized in risk groups

Dose adjustment based on patient characteristics

Dose adjustment based on plasma levels

Identification of gaps in the knowledge on PK and PD measurements

Future ways on how knowledge can be obtained

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Fixed dose dabigatran demonstrated advantages over well controlled warfarin (RE-LY)

These findings were confirmed by large independent analysis of real world evidence

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Information Covered in Current Pradaxa European SmPC

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- **Information in the EU label on dosing based on patients characteristics**
- 110 mg bid: age over 80 years or concomitant use of verapamil
- 110 mg bid or 150 mg bid depending on thromboembolic and bleeding risk.
- Risk factors: age between 75-80 years, moderate renal impairment, gastritis, esophagitis or gastroesophageal reflux, and other patients at increased risk of bleeding

Patient outcomes using the European label for dabigatran

A post-hoc analysis from the RE-LY database

Gregory Y. H. Lip[1]; Andreas Clemens[2]; Herbert Noack[3]; Jorge Ferreira[4]; Stuart J. Connolly[5]; Salim Yusuf[5]

The availability of data from two randomized dosage groups in RE-LY allowed for a post hoc analysis of the treatment of patients according to their characteristics.

"Adherence to European label results in a meaningful and clinically relevant benefit for dabigatran over warfarin, for both efficacy and safety."

Lip GYH, et al. Thromb Haemost. 2014 May 5;111(5):933-42.

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"*Measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors.*"

Examples of potentially increased risk of bleeding are:

- Suspected overdose
- Acutely ill
- Haemorrhagic event during treatment
- Acute renal failure
- Urgent surgery

Measurement using Coagulation test (aPTT) and CE marked dabigatran calibrated assays (dTT, ECT)

- Threshold concentrations at trough (>200 ng/ml; corresponding to an aPTT ratio > 2-fold upper limit of normal, or aPTT prolongation of about 80 sec) may be associated with elevated bleeding risk
- Several suitable CE marked assays (Hemoclot®, Technoclot®, HemosIL®) available for dabigatran plasma level measurement.

Down Titration can have the Potential to Increase Stroke Risk

Example: Patients with CrCL of 30 to < 50ml/min

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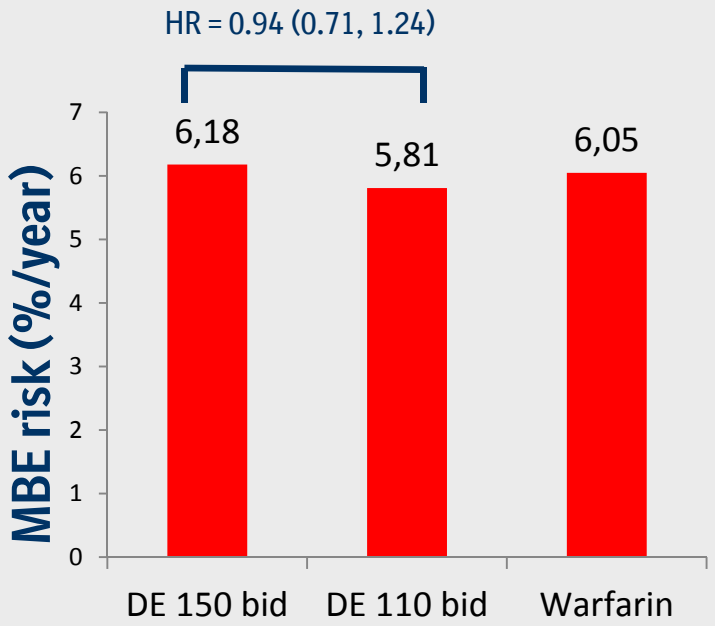
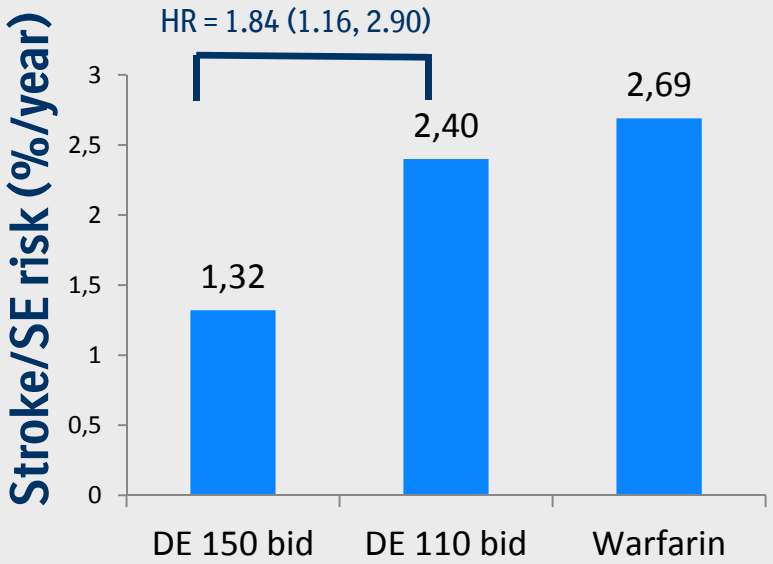
MBE: Relative risk reduction is - 6% if using DE 110 instead of DE150



Stroke/SE: Relative risk increase is +84% if using DE 110 instead of DE150



US Prescribing information 2015 (for DE 150 mg and warfarin), DE 110mg calculated accordingly (data on file), in accordance to Hijazi Circulation 2014;129:961-70.

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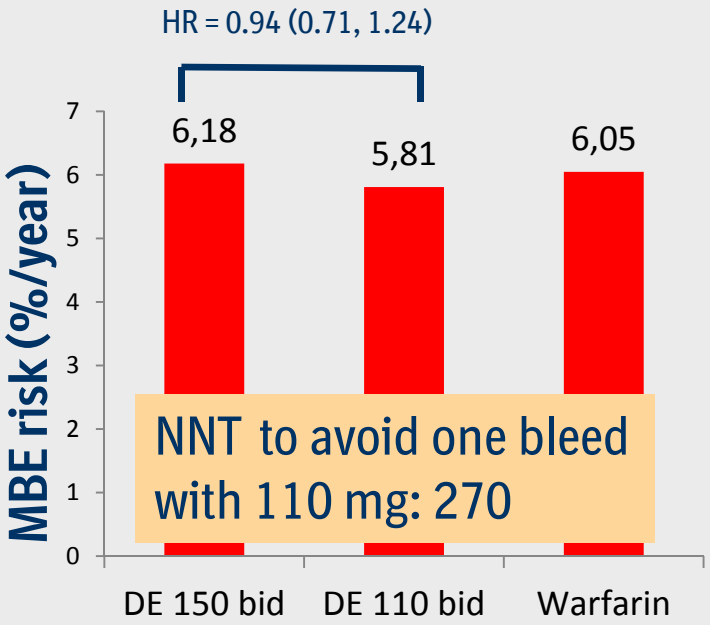

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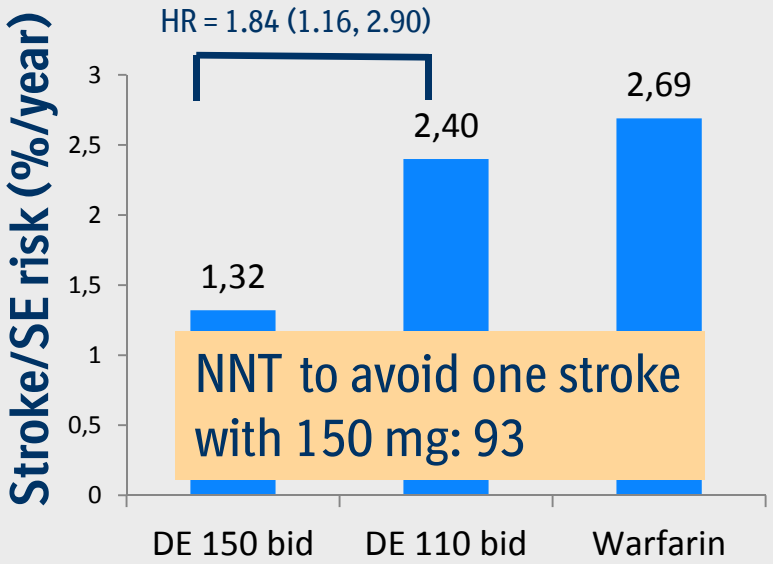

- For every bleed saved in this sub-group, three additional strokes would be expected if using DE 110 mg instead of DE 150

US Prescribing information 2015 (for DE 150 mg and warfarin), DE 110mg calculated accordingly (data on file), in accordance to Hijazi Circulation 2014;129:961-70.

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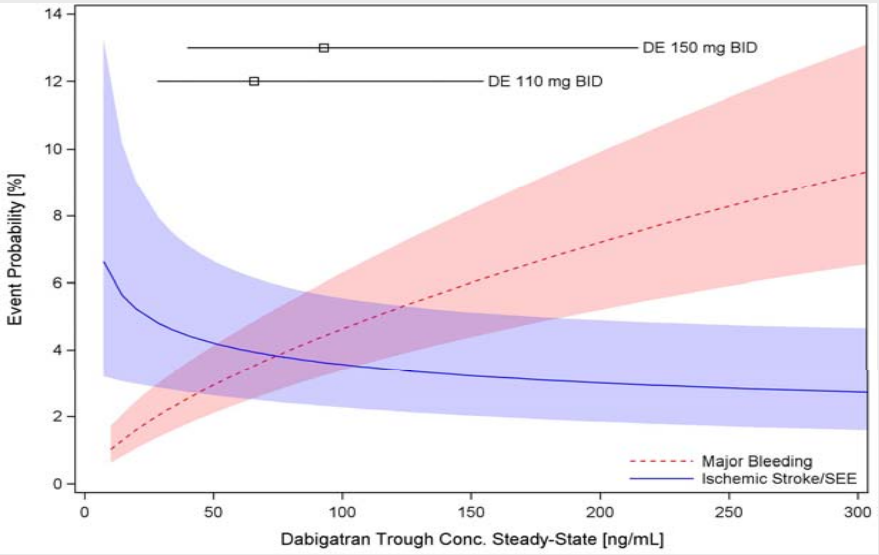
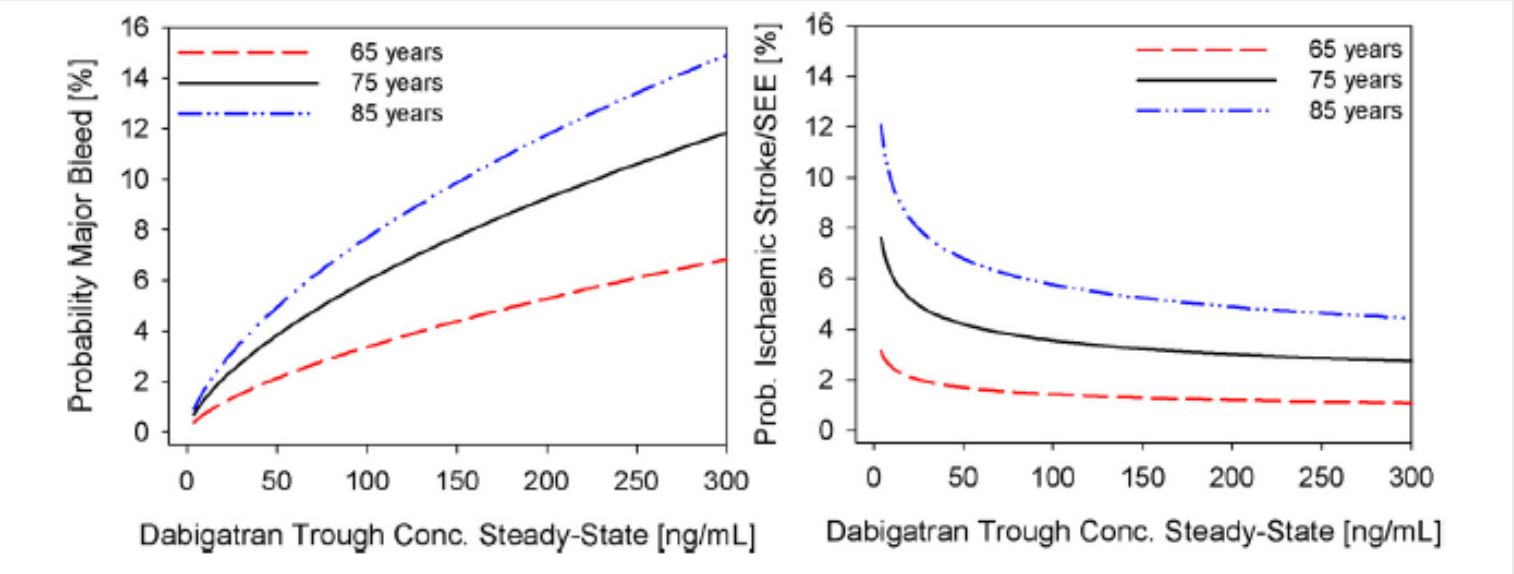
Population-Based PK/PD – Modelled Outcome Analysis



PK/outcome **modelling** for a 72-year-old male AF patient with prior stroke and diabetes.



Reilly PA et al., J Am Coll Cardiol. 2014;63:321-8.

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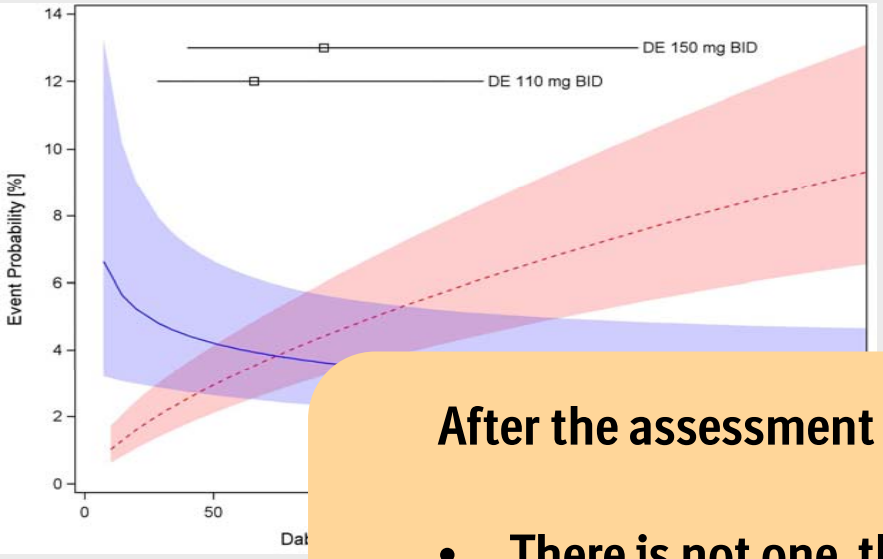
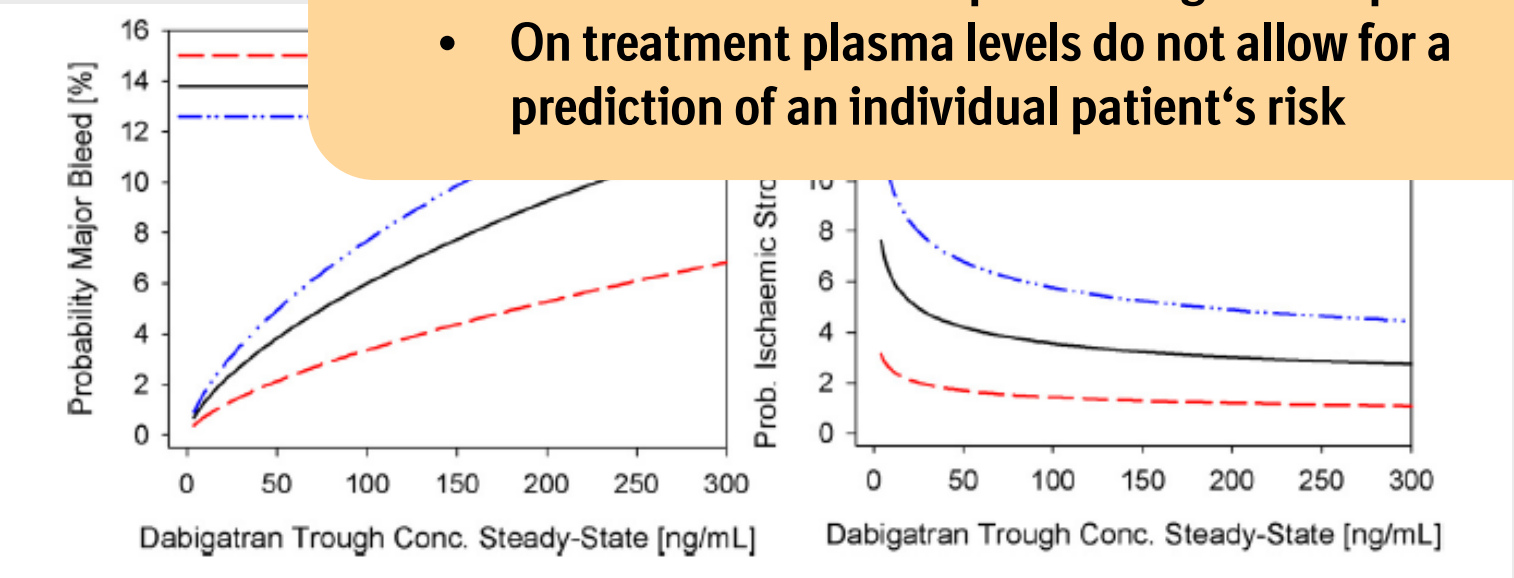


PK/outcome **modelling** for a 72-year-old male AF patient with prior stroke and diabetes.

After the assessment of all data it became evident that:

- **There is not one therapeutic range for all patients**
- **On treatment plasma levels do not allow for a prediction of an individual patient's risk**



Reilly PA et al., J Am Coll Cardiol. 2014;63:321-8.

If there were one ideal plasma level for a certain subgroup, could we identify this level?

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- **Post marketing registry:** It will not be possible to establish a reliable PK/outcome relationship in such a study as PK samples cannot be collected systematically
- **Small PK/PD study:** Isolated PK samples from individual patients without outcome data will not help to give a recommendation on optimal plasma levels
- **Pragmatic outcome trial (e.g. small sample size, safety only) with target plasma level:** Cannot answer the question as it will not be powered for safety **and** efficacy
- **Large outcome trial on dose adjustment to target plasma level in subgroups:** This is the only way to clarify the question, sample size > 15000, duration several years, would only provide answer on **one** subgroup of patients

Best use of Dabigatran

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Future Ways on how Knowledge can be Obtained
Ongoing Programs to Gain Further Knowledge

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- Patients with AF after coronary stenting on dual antiplatelet therapy are at high risk of bleeding and stroke
  Pradaxa trial RE-DUAL investigates if single antiplatelet therapy provides better safety and efficacy

- Patients with embolic stroke of unknown source (ESUS) are at high risk of recurrent events
  Pradaxa trial RE-SPECT ESUS investigates if recurrent stroke can be prevented

- Patients undergoing AF ablation are at high risk of stroke and bleeding if being bridged
  RE-CIRCUIT investigates the use of uninterrupted dabigatran in this population

- Anticoagulated patients who require urgent surgery or present with bleeding were lacking a specific reversal agent
  RE-VERSE AD (idarucizumab for reversal of anticoagulation) has led to approval (US) and positive opinion (EU) of Praxbind

- VTE in children as part of the pediatric investigation plan
  Clinical outcome and PK data generation

Summary

- Pradaxa treatment is safe and efficacious when used according to label
- Plasma level measurement for certain clinical situations is covered in current label
- Pragmatic PK trials are not useful to provide guidance for testing for high risk individuals
- A single large outcome trial will not deliver timely answers on optimal plasma levels for all pertinent subgroups
- Ongoing clinical trials on dabigatran and the reversal agent (positive opinion for Praxbind, Sept. 2015; approval US, Oct. 2015) will help to further enhance safety and efficacy for patients