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What can we do now and what are the gaps in our knowledge?

The direct thrombin inhibitor (dabigatran etexilate)

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Declaration of Interests

- Employment: No interests declared
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What is in the current Product Information?

Pradaxa does not in general require routine anticoagulant monitoring. However, the measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. The INR test is unreliable in patients on Pradaxa and false positive INR elevations have been reported. Therefore INR tests should not be performed. Diluted thrombin time (dTT), ecarin clotting time (ECT) and activated partial thromboplastin time (aPTT) may provide useful information, but the tests are not standardised, and results should be interpreted with caution (see section 5.1).

Table 2 shows coagulation test thresholds at trough that may be associated with an increased risk of bleeding (see section 5.1)

Table 2: Coagulation test thresholds at trough that may be associated with an increased risk of bleeding.

Test (trough value)	Indication	
	pVTEp orthopaedic surgery	SPAF and DVT/PE
dTT [ng/mL]	> 67	> 200
ECT [x-fold upper limit of normal]	No data	> 3
aPTT [x-fold upper limit of normal]	> 1.3	> 2
INR	Should not be performed	Should not be performed

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What is in the EPAR?

- Coagulation tests relevant for dabigatran available at time of approval of AF indication were discussed
- It was concluded that coagulation tests
  - can only be used to define the theoretical risk of bleeding at a certain PD measure, but not to define a therapeutic range for the prevention of stroke
  - can be used to decrease the dose in case of increased exposure but never to increase the dose in case of lower exposure
- For the AF indication, 200 ng/mL at trough was agreed as not to be exceeded because of increased risk of bleeding
- Only limited PK/PD testing was undertaken in the DVT/PE (treatment and prevention) programme
  - Eventually, the same posology and recommendations regarding coagulation tests as for the AF indication were applied

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Reilly PA et al. J Am Coll Card. 2014 Feb 4;63(4):321-8

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Antithrombotic Therapy

The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)

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Ridgefield, Connecticut; Biberach and Saarbrücken, Germany; Hamilton, Ontario, Canada; Wynnewood, Pennsylvania; and Uppsala, Sweden

Objectives The goal of this study was to analyze the impact of dabigatran plasma concentrations, patient demographics, and aspirin (ASA) use on frequencies of ischemic strokes/systemic emboli and major bleeds in atrial fibrillation patients.

Background The efficacy and safety of dabigatran etexilate were demonstrated in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, but a therapeutic concentration range has not been defined.

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Background

- Reilly et al present analyses of data derived from the RE-LY study (Connolly SJ et al. Dabigatran versus warfarin in patients with atrial fibrillation. NEJM 2009 Sep 17;361(12):1139-51)

- The RE-LY study found that in AF patients (n=>18,000):
  - DE 110 mg bid was associated with significantly less bleeding than both warfarin (INR 2-3) and DE 150 mg bid
  - Compared with DE 110 mg bid, exposure to dabigatran was increased by 36% with DE 150 mg bid resulting in
    - 39% reduction in strokes/systemic emboli
    - 16% increase in major bleeding

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Background, continued

- Plasma concentrations of dabigatran vary depending on factors such as absorption and renal function.

- It is unknown whether there is a single concentration range where the balance between thromboembolic events and bleeding events is optimal for all AF patients.

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Objectives – Reilly et al

- To explore the association between plasma concentrations of dabigatran and efficacy and safety outcomes.

- To identify factors affecting the variability of plasma concentrations of dabigatran and their impact on outcome events in AF patients with an indication for oral anticoagulation.

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Methods – Reilly et al

- In the RE-LY study, peak and trough samples at steady state were collected for determination of drug concentration at 1-month post-randomisation in all DE subjects who gave consent to participate (no. participants approx. no. of recruited subjects).
- Approximately 12% of samples were excluded from evaluation due to questionable records in blood sampling date/time or in administration date/time.
- A PK substudy provided additional samples taken at 3, 6 and 12 months from ~2,000 subjects.
- Merged data were analysed.

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Methods, continued – Reillly et al

- Logistic regression of events (ischaemic stroke/SEE) and major/minor bleeds and associated log-transformed trough plasma concentrations was performed with and without covariates.

- Covariates: Creatinine Clearance, Age, Gender, Body Weight and several others

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Results – Reilly et al

- Plasma concentrations of dabigatran were available from
  - Peak: n~9,000 (76% of randomised patients)
  - Trough: n~8,500 (70% of randomised patients)
    - DE 110 mg bid: Geometric mean ~65 ng/mL
    - DE 150 mg bid: Geometric mean ~90 ng/mL

- Geometric mean trough concentrations were 41% higher for the DE 150 mg bid dose compared with the DE 110 mg bid dose

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Results, continued – Reilly et al

- Impact of covariates
  - Renal function
    - Moderate renal impairment: ~2.3-fold higher trough conc.
    - Mild renal impairment: ~1.5-fold higher trough conc.
  - Age
    - Plasma conc. of dabigatran increased by 68% in patients age ≥75 years compared to those < 65 years (renal function highly correlated with age)
  - Gender
    - Plasma conc. in females ~30% higher than those in males
  - Body Weight
    - < 50 kg associated with plasma conc. 21% higher than for subjects 50-100 kg – and 53% higher than for subjects ≥ 100 kg

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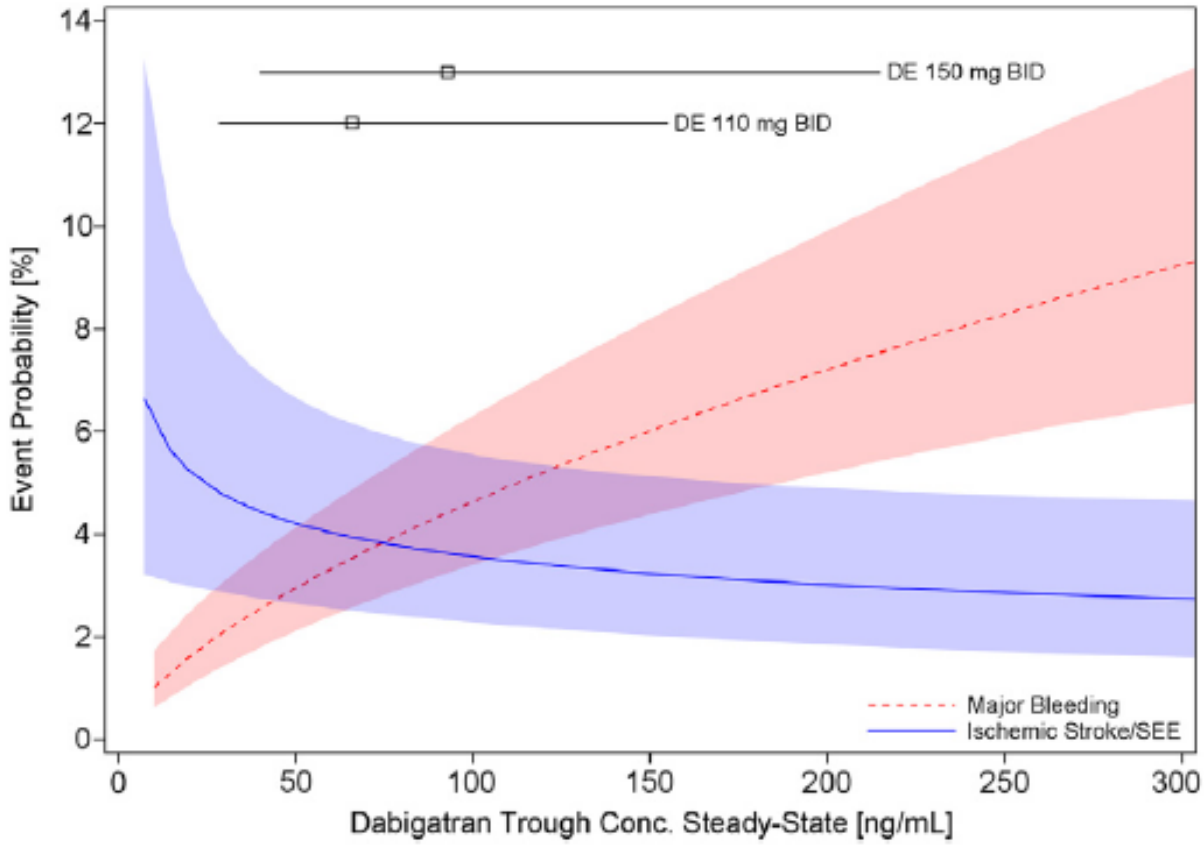
Results, continued – Reilly et al

- Plasma concentration and outcome events
  - Subjects experiencing no bleeding events: ~75 ng/mL
  - Subjects experiencing a major bleed: 55% higher trough concentrations (~116 ng/mL) than subjects without bleeding events
    - Haemorrhagic stroke (n=11): 144 ng/mL
    - Ischaemic stroke/SEE: no difference in plasma concentration
- Age and Creatinine Clearance had similar predictive values as covariates – highly correlated.

Results, continued – Reilly et al



- Probability of major bleeding event and ischaemic Stroke/SEE vs. trough plasma concentration of dabigatran

Reilly PA et al. J Am Coll Card. 2014 Feb 4;63(4):321-8

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Discussion – Reilly et al

- The risks of major bleeding and ischaemic stroke/SEE after dosing with DE 110 mg bid or DE 150 mg bid in patients with AF were related to trough concentrations of dabigatran.
- Covariates of importance: renal function, age, gender, body weight.
- Concentration range for either dose in RE-LY ranged over 5-fold for the 10th and 90th percentiles.
- Assays of dabigatran concentrations have limited availability.

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Conclusion – Reilly et al

- Both doses of DE in RE-LY were associated with a more than 5-fold variation in plasma concentrations.
- Renal function was the predominant patient characteristic that determined plasma concentrations.
- Safety and efficacy outcomes were correlated with plasma concentrations of dabigatran, age being the most important covariate.
- No single plasma concentration range provides optimal benefit-risk for all patients.
- The balance between stroke risk and bleeding risk varied with concentration, suggesting that a subset of AF patients may improve their benefit-risk balance with DE by a tailoring of the dose in relation to patient characteristics.

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Study strengths and limitations – Reilly et al

- Strengths
  - Over 70% of the >12,000 patients randomised to DE had at least 1 plasma sample on treatment
  - Benefit-risk assessment is based on the primary safety and efficacy outcomes
- Limitations
  - Not all patients contributed a blood sample
  - Medication compliance was not assessed in the analysis
  - RE-LY study participants were randomised to DE dose without consideration of their renal function (subjects with severe renal impairment were excluded from RE-LY)

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Questions

- Arbitrary therapeutic range for plasma concentration 50-200 ng/mL?
- Given the known variation of plasma concentration analyses of dabigatran, how many measurements would be sufficient?
- Choosing between DE 150 mg bid or DE 110 mg bid based on clinical characteristics as described in the label results in similar levels of drug exposure
  (Chan NC et al. J Thromb Haemost 2015 Mar;13(3):353-9)
- Subgroups of patients may benefit from monitoring of plasma concentrations and/or dose tailoring
  (Douxfils J et al. Expert Opin Drug Saf. 2015 Aug;14(8):1283-9)

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Thank you for your attention